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BRAIN POTENTIALS AND VOLUNTARY MUSCLE ACTIVITY IN MAN*

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IT HAS long been known that the central grey matter possesses an inherent rhythmicity which is reflected in discharges along motor neurons to voluntary musculature. Horsley and Schäfer, in 1886,[16] found that muscular contractions elicited by cortical stimulation in dogs, cats, rabbits and monkeys exhibited a rhythm independent of the frequency of stimulation. This rhythm, which they attributed to some fundamental property of the higher centers, was usually about 10 per second, or between 8 and 13 per second. Schäfer,[26] from records of muscle thickening during voluntary contraction in man, observed a rhythm of 8 to 13 per second with an average of 10 per second. This same frequency appears again in the early studies of the speed of single and repeated voluntary movements in man by von Kries (1886).[21] He found that voluntary rhythmic alterations of finger movement could not exceed about 10 per second.

Hoffman and Strughold[15] have recently shown that muscle action potentials in man in response to rhythmic stretching of the forearm at a frequency of 55 per second were not continuous, as might be expected from the simple "Eigenreflex." They observed rhythmic modulations in the amplitude of the train of action potentials. The major rhythm of this modulation, or interruption, occurred at a frequency of about 10 per second, demonstrating that the reflex centers in the cord were apparently undergoing a fluctuation in excitability at about this frequency.

According to Travis and Hunter,[27,28] the major tremor rate in normal individuals, as recorded from the end of the finger, is between 8 and 12 per second and is accompanied by rhythmic volleys or "envelopes" of muscle action potentials preceding slightly each tremor movement. A secondary rhythm of 40 to 50 per second was found to be superimposed upon the major 10 cycle frequency.

These results may have acquired a new significance in the light of Berger's discovery that the predominant potential rhythm of the cerebral cortex in man is also at about 10 per second, with a range of frequencies very similar to that found by Schäfer in the super-imposed tremor during voluntary contraction in man. Cortical potential rhythms between 9 and 12 per second have also been found characteristic of cortical electrograms of the dog and the monkey.[5,2] Adrian[3] has recently demonstrated that certain potential waves from the motor cortex of the monkey are directly associated with excitatory processes to the motor neurons resulting in movements of the limb muscles. It appears from these studies that certain central neurons give rise to slow

* Research conducted with the aid of a grant from the Rockefeller Foundation.

rhythmic electrical disturbances, either spontaneously or in response to stimulation, which may be related in some way to excitatory processes which reach motor neurons innervating voluntary musculature.

It is the purpose of the present study to investigate further, in man, the relationship between rhythmic cortical potentials as recorded through the unopened skull and certain rhythmic characteristics of involuntary contraction in striate muscle. We have approached this problem through simultaneous records of normal brain potentials with records of normal finger tremor and muscle action potentials, in addition to studies of pathological tremor in paralysis agitans and the rhythmic clonic movements in relation to seizure waves in epilepsy.

TECHNIQUE

Four balanced completely push-pull, condenser coupled amplifiers leading to a four element Westinghouse oscillograph were used for independent recording from different head regions and for recording muscle potentials, tremor, and brain potentials simultaneously on continuous photographic recording paper. Muscle potentials were recorded either from concentric needle electrodes or from surface electrodes on the skin.

In order to obtain tremor movements with a minimum of distortion, one finger was held by the subject in a slightly extended position free from any mechanical attachments. The rest of the hand and fingers were held firmly in a frame. Two methods of recording were used, (1) a very light piece of metal was taped to the end of the finger which was placed in the magnetic field of a head-phone, the potentials set up in the phone coils being led to the input of the amplifier, and (2) the finger was placed in a wedge-shaped beam of light focused on a Weston photronic cell which was connected to the amplifier. Each of these recording devices was capable of detecting finger movements which were scarcely visible. The first method of recording exaggerated the more rapid components of the tremor to some extent so that it was abandoned in favor of the photo-cell recording for the majority of the experiments. The photo-cell method also eliminated the continuous down pull on the finger exerted by the magnetic field. The sensitivity of the tremor recording devices was adjusted so that there was no electrical interference with the amplifiers used for recording the brain and muscle potentials.

The technique used for the bipolar or monopolar records of brain potentials from electrodes on the scalp surface is similar to that described in previous publications (18, 19).

Normal brain potentials and tremor movements

Tremor movements of the fingers were found to have a major rhythm at frequencies between 8 and 13 per second in 10 normal subjects, with an average frequency of about 10 per second.* A secondary tremor frequency between 17 and 30 per second was also present with an average of about 25 per second. These frequencies correspond very closely to the alpha and beta rhythms previously reported as characteristic of cortical potentials from over

* In some subjects the average frequency from the little finger was 0.5 to 1.0 cycle per second slower than that from the index finger which showed that mechanical effects on tremor frequency were not without importance. Precautions were taken to limit the recording to only the vertical movements of one finger which avoided gross mechanical distortion from hand movements and the interference from the other digits. Under these conditions those subjects with a fairly large tremor showed the same frequency in each of the four fingers suggesting that the finger movements were representing actual muscle tension rhythms. This was confirmed in records of muscle potentials which showed groups of muscle potential discharges at the tremor frequencies as reported by Travis and Hunter (27, 28). We were not able to ascertain from our records of muscle potentials taken with needle electrodes, whether the grouping was made up of interrupted trains of unit discharges or volleys. The latter is more probable. Experiments are now in progress to elucidate this point.

the motor region.[19] The similarity in frequencies of tremor movement and brain potentials from the motor region, as compared to the alpha rhythm from the occipital region in subject E. R., is shown in Fig. 1-A. The groupings of muscle action potentials from the extensor and the flexor (sublimus) muscles of the digits in this subject also showed, at times, a 10 per second rhythm and a 25 per second rhythm corresponding to the two components of the tremor. Subject E. R. showed the same frequency of alpha rhythm from the motor and occipital regions corresponding also to the slow component of the tremor. In subjects who showed a difference between the occipital alpha and the motor alpha rhythm, the tremor showed a closer correspondence with potentials from the motor region. For example, in subject M. O. (Fig. 1B), the occipital alpha rhythm was about 9.5 per second while the

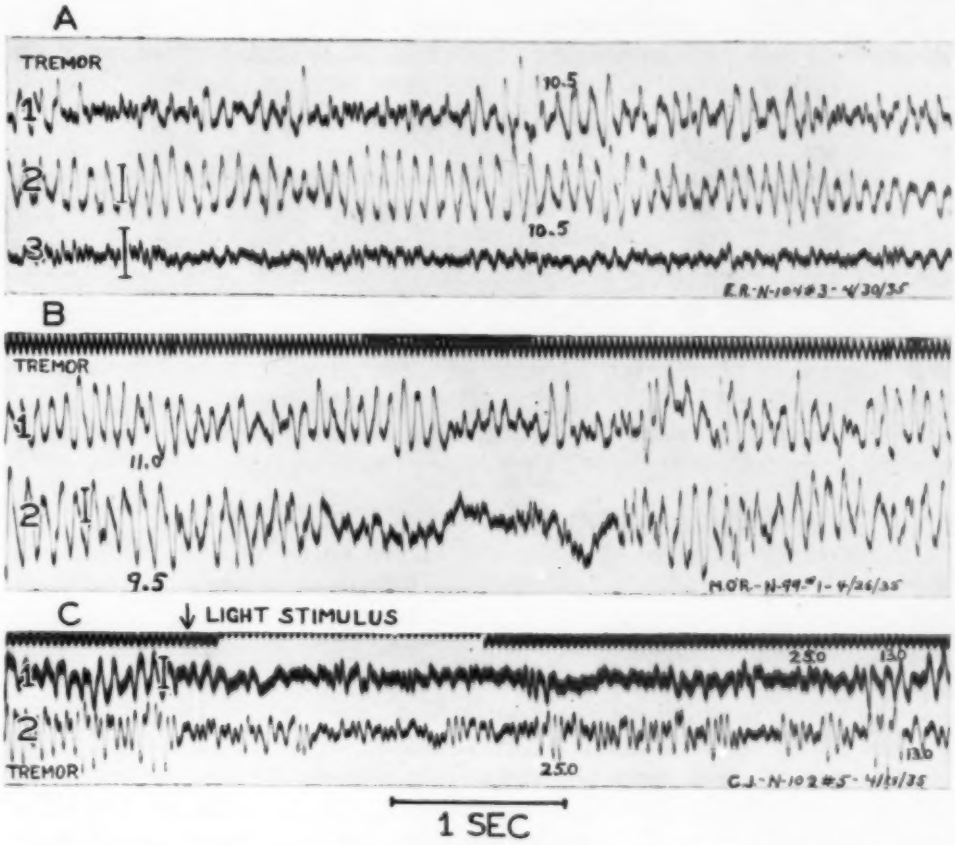

FIG. 1. Normal Tremor and Brain Potentials. A. Subject E. R. showing the slow (10.5 per sec.) and the rapid (25 per second) rhythm in the tremor from the right index finger (1) corresponding to the frequencies found in the Occipital (2) and precentral (3) brain potentials. B. Subject M. O. showing left index finger tremor at 11 per second (1) at the same time as occipital alpha rhythm (2) at 9.5 per second. C. Subject C. J. showing right precentral brain potentials (1) with left second finger tremor. The tremor shows the same frequencies and a similar response to light stimulation as the brain potentials.

slower components of the potential rhythms from the motor region were about 11 per second which corresponded with the tremor frequency.

The arrest of the occipital alpha rhythm, either "spontaneously" or by light stimulation of moderate intensity, may be associated with very little change in the tremor as shown in Fig. 1B. We have occasionally observed, however, changes in the finger tremor with unexpected auditory stimulation which parallel quite closely the changes in the potential rhythms from over the precentral region as shown in Fig. 1C. In some cases an unexpected auditory stimulus caused an arrest of the tremor for about one-half second followed by a sudden facilitation of the tremor to about twice its former magnitude, returning to its normal magnitude after about five seconds.* The potentials from the motor cortex were usually decreased in magnitude during the period of augmentation of the tremor and returned to their normal amplitude and regularity as the tremor decreased to its normal level. In subjects with little or no slow rhythm from the motor cortex, as in the example given in Fig. 2C, no relationship can be shown between the brain potential rhythms and tremor frequency. Since the absence of the slow rhythms and the presence of low amplitude higher frequency potentials (40 to 60 per second) is characteristic of a condition of cortical excitation,[17] it seems that either the true frequency of cortical discharge is not obtained under these conditions, due to desynchronization, or the control of the tremor frequency is taken over by sub-cortical motor centers.

It appears from these results that tremor movements and brain potentials from over the precentral cortex may correspond closely in their frequencies and response to stimulation under certain conditions in normal individuals, but the absence of correspondence in other cases shows that there is no necessary relationship between the frequency of cortical potentials and that of the tremor movements.

The effect of sleep on tremor and brain potentials

Since brain potential rhythms are known to be altered markedly in sleep,[13, 25] it was thought that simultaneous records of tremor movements and brain potentials during sleep might help to clarify the functional relationship between these two phenomena.

Brain potentials from the frontal, precentral, and occipital regions of the head were recorded simultaneously with finger tremor movements during sleep in three normal individuals. In one of these individuals the tremor records during sleep were not sufficiently regular for consideration, due chiefly to technical difficulties. Examples of results from the other two subjects are given in Fig. 2. In subject H. C. the waking record (A) showed a relationship between the potentials from the frontal pairs of head electrodes (1 and 2) and the tremor from the right index finger (4) with a predominate frequency of 10 to 11 per second. The occipital alpha rhythm (3), however,

* An augmentation of the alpha rhythm from the motor region is also occasionally observed in response to stimuli which causes a complete arrest of the alpha rhythm from the occipital region (19).

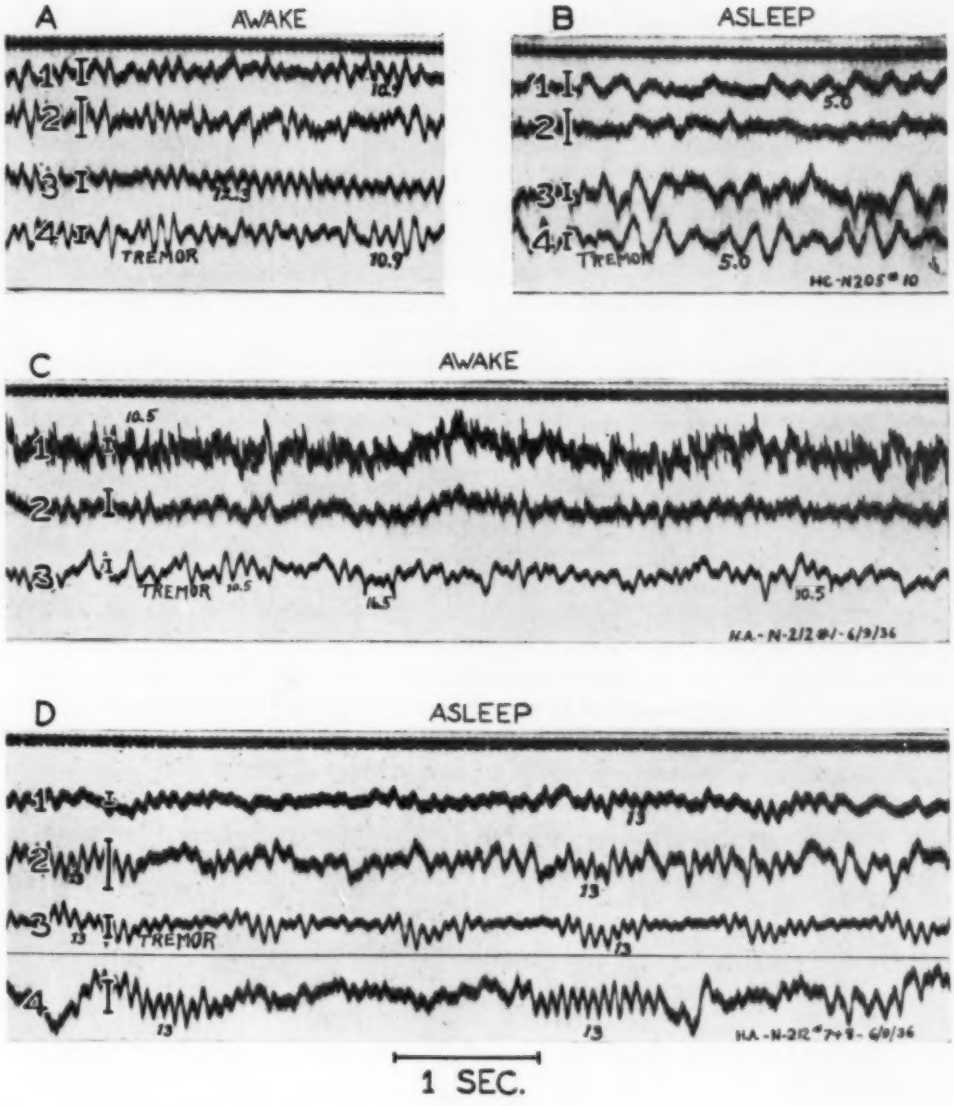

FIG. 2. Brain Potentials and Tremor During Sleep. The first records show correspondence between tremor frequencies from the right second finger (4) and brain potentials from the left frontal region (1) and lack of correspondence with occipital brain potentials from subject H. C. awake (A) and asleep (B). The second two records, from subject H. A. awake and asleep, shows little correspondence between either left precentral (1) or left occipital (2) brain potentials and right second finger tremor (3) awake but a remarkable correspondence between brain potential frequencies (1, 2, and 4) and tremor (3) during sleep.

was above 12 per second, showing little correspondence with the tremor rate. During sleep (B) both the tremor rate and the brain potential rhythms decreased to 5 per second. The second subject (H. A.) awake (C) showed little correspondence between tremor (3) and brain potential rhythms (1 and 2). (Former experiments on this subject had shown a much closer correspondence.) The tremor also was quite irregular showing possible frequencies at about 10 and 16 per second. During sleep, however, this subject showed a remarkable correspondence between tremor and brain potential rhythms with a characteristic frequency of 13 per second in each. This shows that the "sleep rhythm" or "spindles" of Loomis, Harvey and Hobart[25] may also be found in tremor movements. These changes in both tremor and brain potential frequencies as a result of sleep show a close functional relationship between cortical potential and tremor rhythms under these conditions.

One presumably normal subject, F. T., a female nurse 27 years of age, with no recognized neurological disorder, was selected for study because of a somewhat exaggerated regular tremor in both hands. Recording with the photoelectric cell method, it was found that the same frequency of tremor, 6 to 7 per second, was present in each finger of either hand. Placing the hand palm down or palm up and changing the amount of voluntary tension of the finger did not alter the tremor frequency. The brain potential rhythms from frontal, precentral, and occipital bipolar leads showed no correspondence with the tremor frequency at the beginning of the experiment as shown in Fig. 3A. The subject was nervous and apprehensive at this time and showed very little slow rhythm in the brain potentials from either bipolar or monopolar leads except for an occasional group of low amplitude occiptial alpha potentials at a frequency of 9 to 10 per second. The tremor, however, was regular and continuous at a frequency of 6.8 per second.

After about one-half hour the subject appeared much more relaxed and less apprehensive about the experiment. The tremor continued as usual at 6.5 to 7.0 per second. Bursts of large amplitude rhythmic potentials, at the tremor frequency, now appeared in the brain potentials from all regions. Each burst lasted for about 3 seconds. They were more prominent from the frontal and central regions. Excitation of the subject at this time with an unexpected visual or auditory stimulation would produce again the excited brain potential picture with no large amplitude slow potentials. The tremor would continue undisturbed. It appears as if the continuous rhythmic subcortical discharges responsible for the tremor could momentarily control the synchronized beat of the cortical cells if the cortex was not sufficiently activated. The possibility of independent subcortical control of tremor which may momentarily take over control of cortical potential rhythms is demonstrated in this subject.

Paralysis agitans

Two unilateral paralysis agitans patients were made available for study through the kindness of Dr. Westcott of Butler Hospital. These patients

showed no mental deterioration and had a slight tremor, within normal limits, on the right side. The digits of the left hand showed the continuous gross tremor of 4 to 5 per second, typical of patients with this disorder. Sample records of tremor movements from the index finger on the unaffected side taken together with brain potentials are shown in Fig. 3C. The brain potentials showed the typical normal alpha rhythm between 8 and 10 per second and a beta rhythm between 20 and 30 per second from either hemisphere.

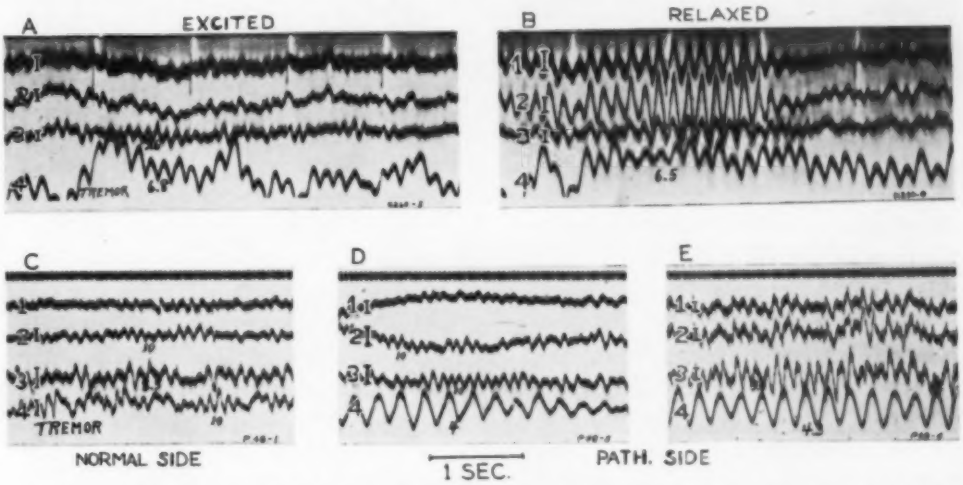

FIG. 3. Brain Potentials and Abnormal Tremor. Records A–E brain potentials from frontal, precentral, and occipital head regions are shown in 1, 2, and 3 with finger tremor in 4. A and B are from subject H. T. excited with no correspondence between tremor and brain potentials and relaxed with large bursts of brain potentials at tremor frequency. C–E from unilateral paralysis agitans, patient W., showing correspondence between tremor and brain potentials on normal side (C) with no correspondence on affected side (D and E). Calibration lines equal 20 microvolts.

The tremor from this side also showed approximately the same combination of frequencies. The bipolar (D) and monopolar (E) records of brain potentials showed no relationship with the tremor from the affected side. That the tremor movements give a faithful picture of muscle activity was shown by the bursts of muscle potential from the flexor digitorum profundus preceding slightly each tremor movement.

In two other cases of more advanced bilateral paralysis agitans, short bursts of large amplitude brain potentials would occur occasionally at the tremor frequency in a manner similar to that described above for the "normal" subject F. T.

These cases demonstrate that the pathological process of paralysis agitans may be localized, in the unilateral cases, producing continuous rhythmic discharges which do not affect the tremor of the unaffected side nor do they appear to be related to cortical potential rhythms as is the normal tremor. In the more advanced cases the spontaneous rhythms of the cortex may be controlled, to a certain extent, by the more extensive subcortical discharges.

Clonic movements and seizure waves in petit mal epilepsy

Seizure waves, led off directly from the motor cortex in rabbits and monkeys during convulsions brought on experimentally by means of convulsant drugs or over-breathing, were shown by Kornmüller to have a fairly definite relationship to the frequency of clonic movements.[20] The relationship was not perfect and seizure waves could be detected at times when there was no evidence of any overt convulsion. Gibbs, Davis, and Lennox[13] had the impression that the frequency of clonic convulsive movements in epileptic patients was similar to that of the 3 per second discharges found from the cortical potentials as recorded through the skull. They report the presence of seizure waves in some patients without any detectable convulsive movements and also that seizure waves usually precede the convulsive movements at the beginning of an attack. Foerster and Altenburger[11] have obtained seizure waves directly from the motor cortex in man during brain surgery simultaneous with a Jacksonian attack of the right arm. Since muscle activity was not recorded with the seizure waves in these patients the precise relationship between the two phenomena is in need of further study.

Simultaneous records of brain potentials, clonic movements, and muscle potentials were obtained from three petit mal epileptic patients who usually showed minor motor manifestations at some time during the attack. Cortical potentials were taken from bipolar leads over the left precentral region. Clonic movements of the right index finger were recorded by the photo-cell method. Muscle potentials were obtained chiefly from silver wire electrodes on the skin surface over various arm and leg muscles. Concentric needle electrodes in the muscle did not prove satisfactory due to displacements of the base line with the muscle movements and to the difficulty of getting the needle over units which would be activated during the clonic contractions.

After the electrodes were placed, seizures were brought on by over-breathing. In all seizures, one to ten of the "spike" and slow wave patterns would appear before clonic movements could be detected. If the movements involved muscles from which the recording was made, each seizure wave might be accompanied by a burst of muscle potential after a latency of 50 to 60 milliseconds and by a clonic finger movement after a latency of about 100 milliseconds as shown in Fig. 4A and B. Little importance can now be attached to these latencies since it is often very difficult to determine from what part of the complex seizure wave they should be measured. They were measured from the beginning of the first "spike" which, in some cases, seemed to initiate the epileptiform discharge.

Simultaneous action potential records from the extensor digitorum and the gastrocnemius in one experiment gave apparent latencies of about 50 milliseconds to the gastrocnemius and about 100 milliseconds to the extensor digitorum (Fig. 4A). The aspect of the seizure wave from which this latency was measured to the gastrocnemius probably did not represent the same part of the cortical discharge for the extensor. This delay of about 50 milliseconds in the arrival of the impulse from the leg to the arm musculature may be

largely due to the conduction time from the leg to the arm area in the cortex since conduction velocity of such waves in the cortex has been shown by Adrian[3] to be from 5 to 50 or 60 cms. per second in anaesthetized animals.

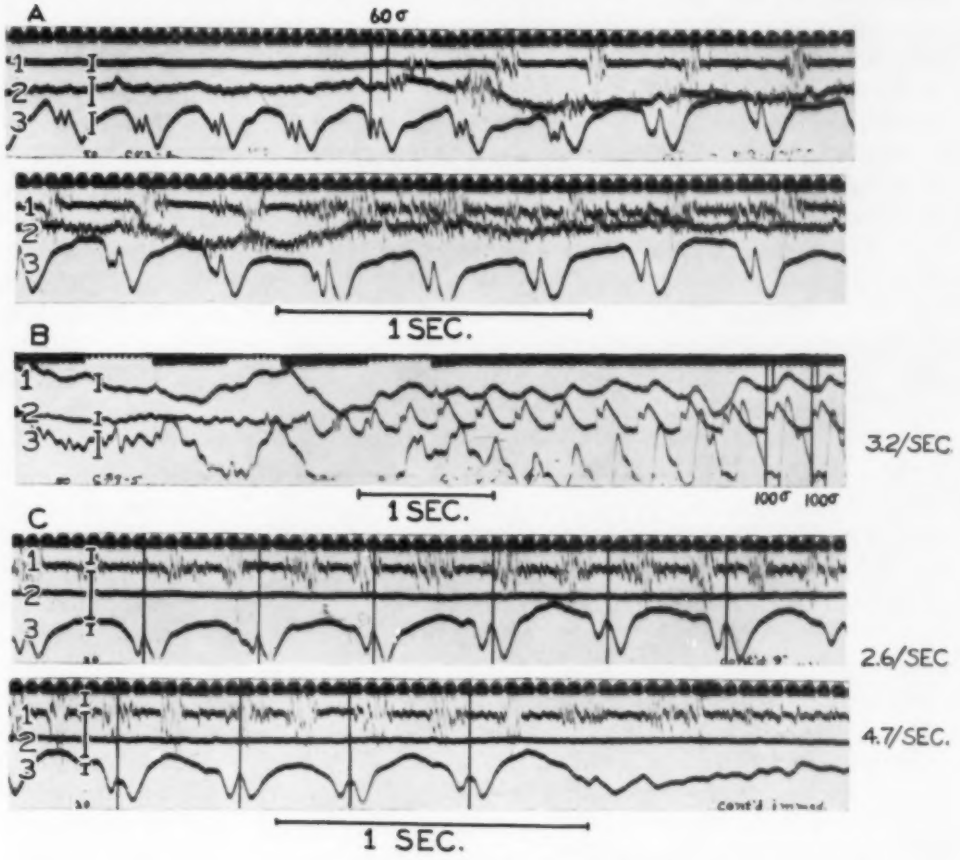

FIG. 4. Seizure Waves, Muscle Action Potentials, and Clonic Movements in Petit Mal Epilepsy. A. Patient H. T. during an attack. (1) Right digit extensor and (2) right gastrocnemius muscle potentials from surface electrodes. (3) Left precentral brain potentials. B. Same patient at beginning of another attack. (1) Potentials from needle electrode in right flexor of digits showing slow movement artifacts with muscle potentials scarcely visible. (2) Left precentral brain potentials. (3) Right index finger movements (photo-cell method). C. Same patient at end of another attack which did not involve the gastrocnemius. (1) Muscle potentials from right digit extensors and (2) right gastrocnemius (surface electrodes). (3) Left precentral brain potentials (bipolar leads). Calibration lines in A and B equal 50 microvolts, and in C equal 20 microvolts.

If one assumes that the conduction velocity may be 100 cms. per second in the unanaesthetized cortex this would imply a distance of about 5 cms. between the arm and leg areas which is not far from the right order of magnitude.

In the three patients used in this study, the convulsive movements

would play over the body musculature from one group of muscles to another throughout the attack in a manner which varied from one attack to another so that only in certain attacks could the above relationships between seizure waves and muscle activity be demonstrated. All attacks were accompanied by seizure waves but some attacks would miss completely certain muscle groups from which records were being taken. Also, occasionally, the bursts of muscle potential would occur at a frequency independent of the seizure waves as shown in Fig. 4C. In this example the seizure waves were at a frequency of about 2.6 per second, while the bursts of muscle potential were about 4.7 per second showing no relationship with the cortical discharges as recorded through the skull. This suggests the possibility that other nerve centers, which are apparently out of step with the cortical areas from which the potentials were obtained, may take over the control of the rhythmic muscle movements during the epileptic attack and that cortical potentials recorded through the skull from over the precentral region do not necessarily signalize excitatory processes reaching these final motor pathways.

Discussion

It is difficult to arrive at definite conclusions from the above findings due to our lack of knowledge regarding the relationships between various efferent centers within the central grey matter which might affect impulses reaching the final common pathway especially with regard to spontenaous discharges in tremor or convulsive movements. The potentials recorded from bipolar leads on the scalp over a part of the cortex just anterior to the central fissure are almost certainly of cortical origin since potentials from deeplying regions could not be detected in this manner. However, the precise cortical origin of these potentials is not known. They may not arise, for the most part, from the motor region proper since it is largely buried within the central fissure. They may obtain their chief components from the premotor and frontal areas. In fact, electrodes farther forward on the head often give potential rhythms quite similar to those obtained from the region of the midsagittal point; both being different from occipital potentials.

Since Dusser de Barenne and McCulloch[9] have found a major spontaneous rhythm of 10 per second arises chiefly from the pyramidal cell layer of the motor cortex in the monkey, one might suppose that these slow potentials represent rhythmic depolarizations of cell surfaces which result in interrupted trains of impulses passing down the pyramidal tracts analogous to the mechanism found by Adrian and Buytendijk[4] in the respiratory centers of the goldfish. Heinbecker[14] has recently demonstrated a similar process in the isolated single heart ganglion cell of *Limulus*. It was surprising to find the beta rhythm of the cortical potentials also in the tremor movements. Jasper and Andrews[19] and Berger[6] have suggested that the beta rhythm may arise from different cortical cells than those producing the alpha rhythm but the mechanism by which these rhythms may also appear in the motor nerve discharges is not clear.

Dusser de Barenne[8] has shown a close functional relationship between spontaneous discharges from the sensory cortex in the monkey and the sensory projection areas in the thalamus. Local strychninization of either the thalamus or cortex would set the thalamo-cortical system "on fire." Gerard, Marshall, and Saul[12] report the same frequencies of spontaneous discharge throughout the visual system in the cat. It would appear from our findings on normal individuals that the spontaneous rhythmic activity of precentral regions of the cortex may be related to rhythmic discharges reaching the final motor pathways when the entire system is "at rest." Cortical activation through afferent channels may either control the tremor, causing an arrest of the slow rhythms in cortical potentials as well as in the tremor (the familiar arrest of paralysis agitans tremor with voluntary movement), or it may cause a dissociation of the cortical and subcortical motor centers, in this case usually causing an exaggerated tremor.

The continuous slow tremor unrelated to cortical discharges found in mild cases of paralysis agitans indicates that the controlling centers in this condition are subcortical; probably related to the striato-pallidal motor system. The breaking through of these subcortical discharges into the cortex when they become more extensive or with a decrease in cortical activation demonstrates the possibility of a close functional interrelationship between the spontaneous activity of cortical and subcortical motor systems. There is apparently a dynamic interplay between cortical and subcortical rhythmically discharging centers in competition, or, under normal resting conditions, integrated for the control of impulses reaching the final common path.

The occurrence of cortical seizure waves previous to the detection of motor disturbance in the epileptic patients shows that the excessive synchronized discharge in these cases first involves regions of the cortex not directly related to the motor system. As the seizure waves increased in magnitude the motor regions were involved, causing volleys of impulses to be set up in the motor nerves for each slow cortical potential. The lack of correspondence between the cortical seizure waves and bursts of muscle action potentials in some cases may be due to the setting up of autonomous discharging centers, probably subcortical, which may take over the control of certain motor pathways.

Kubie's[22] hypothesis in regard to the etiology of spontaneous movements is of particular interest in relation to the results of the present study. Continuous activity is assumed to be maintained in the "silent" areas of the brain by means of impulses conducted in closed circuits or reverberating, self-exciting, neuron chains. Since spontaneous activity, as indicated by rhythmic electrical activity at 10 per second, has been found to be almost continuously present also in the motor area of the monkey and related most specifically to the pyramidal cell layers, it is necessary to assume that continuous activity is not normally confined to Kubie's "silent" areas. The normal control of spontaneous movement appears to be due to the delicate integration of cortical and subcortical discharging centers rather than to the

blocking of discharges from "silent" areas to keep them from getting into the motor system. Spontaneous movements appear to a pathological degree when the synchronized discharge of large masses of cells becomes excessive, as in the epileptic attack; the smaller cell groups losing their individuality of differentiated function.

The continuity of rhythmic activity may not be dependent upon a self-exciting circuit of neurons but to the spontanoeus repetitive firing of units which get into step through mutual facilitation as suggested by Adrian.[1] The nature of the spontaneous activity, although related to impulses arriving from other neurons, may be conditioned to a great extent by the chemical environment of the cells or the "blood stimulus" of Graham Brown,[7] thus determining not only the degree of spread of spontaneous activity as suggested by Kubie, but also being actually the "stimulus" for its maintenance since spontaneous firing of isolated axons may occur in certain rather definite chemical environments.[10,23,24]

Summary

The relation between cortical potential rhythms as recorded through the unopened skull and tension rhythms in forearm musculature has been investigated by means of simultaneous records of finger tremors, muscle action potentials, and cortical potentials in normal subjects and in patients with paralysis agitans and petit mal epilepsy. The frequency of normal tremor movements was found to correspond closely with the frequency of potential rhythms from the regions of the cortex anterior to the central fissure; the major rhythm being at about 10 per second with a minor rhythm of about 25 per second. During normal sleep the tremor rhythms show changes which parallel the changes in cortical potential rhythm; namely, slow rhythms of about 5 per second and bursts of 13 to 14 per second waves.

Sensory stimulation may depress the tremor as it does the cortical potentials or may cause a dissociation between cortical potentials and tremor rhythms, the slow rhythms of the cortex being arrested simultaneously with an increase in amplitude of the tremor. It appears that there is an interrelationship between cortical and subcortical centers in the normal subject at rest which is reflected in the grouping of discharges which reach the final common pathway, but that this relationship may be disturbed by sensory stimulation. Also, the subcortical centers may dominate the tremor movements and become permanently dissociated from rhythmic cortical activity.

In exaggerated bilateral tremor in "normal" individuals there may be no relationship between cortical potential and tremor frequencies as long as the cortex is activated by sensory stimulation or conditions of general excitement or apprehension and the finger maintained in a given postural adjustment. With a decrease in cortical activation the cortical discharges may be periodically controlled by the subcortical activity and also, with a certain type of cortical activation as in voluntary contraction, the cortex may inhibit the subcortical discharges or take over the dominant control of the final common pathways.

The abnormal tremor of 4 to 5 per second in two unilateral paralysis agitans cases did not appear in the cortical potential rhythms which corresponded to the tremor of the unaffected side. In more advanced bilateral paralysis agitans cases the 4 to 5 per second rhythm would appear periodically in the cortical potential rhythms even though the tremor was continuous. It is concluded that the normal functional integration between cortical and subcortical motor centers is interrupted with only a moderate or unilateral involvement of the striato-pallidal motor system. More extensive bilateral involvement may produce subcortical activity which occasionally takes over the control of cortical rhythms.

Cortical seizure waves in epileptic patients may be associated with corresponding bursts of muscle potentials with clonic movements at 3 per second. The latency from the onset of the seizure wave to the muscle potential may be of the order of 50 milliseconds. The lack of correspondence between clonic movements and seizure waves in some attacks indicates that other centers, probably subcortical, may be set into autonomous activity and take over control of certain motor pathways.

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ACTIVATION OF HEAT LOSS MECHANISMS BY LOCAL HEATING OF THE BRAIN*

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OF IMPORTANCE in the maintenance of a relatively constant body temperature are those heat loss activities which are brought into play on exposure to an excessively warm environment and aid in preventing the temperature of the body from becoming elevated above its normal range. In the cat, polypnea and panting are the most easily observed as well as the most important factors in the elimination of excessive bodily heat. Sweating is observed only on the pads of the feet, and peripheral vasodilatation is difficult to measure even with the most delicate thermocouples applied to the skin.

In the cat, panting usually does not occur in response to external heat until there is considerable rise of body temperature. An average rise of 0.78°C. occurred before panting began in a series of 43 cats subjected by Clark (1937) to external temperatures of 40°C., but in five of these cats panting occurred before there was any rise in rectal temperature. The results in these five cats are suggestive of the reflex panting without rise in body temperature which is known to occur in the dog. Acknowledging the possibility that surface receptors may cause reflex panting in the cat, it is certain that the reaction is usually elicited by the elevation of body temperature.

A number of observations have indicated that an elevated intracranial temperature constitutes an effective stimulus for the activation of the heat loss mechanism. Warming the carotid blood entering the head has been shown (Kahn, 1904; Moorhouse, 1911; Hammouda, 1933) to cause sweating, peripheral vasodilatation, and hyperventilation in experimental animals, and the authors have inferred that these effects were produced by direct or central activation of regulating centers in the brain by the rising temperature of the blood.

Some support of this view has been provided by experiments in which parts of the brain have been heated directly, either by warm water passing through a closed tube inserted in or applied to the desired region, or by open irrigation with warm saline. Barbour (1912), Hashimoto (1915) and Prince and Hahn (1918) found a fall in body temperature resulted from heating the corpus striatum in the rabbit and cat, and the first two workers described a peripheral vasodilatation during this procedure. Moore (1918) confirmed the antipyretic action of warming this region but showed that the corpus striatum was not specifically related to the effect, and Sachs and Green (1917) could not observe any constant result of warming or irritating the corpus striatum in various other ways. It has been pointed out by Bazett (1927)

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that the effects obtained by Barbour and others were probably produced at some distance from the site of heating in the corpus striatum because of the high temperatures which had to be used to obtain reactions. Hasama (1929) found a fall in body temperature to result from warming the base of the hypothalamus and preoptic region in the cat, and observed a profuse sweating on the footpads during this procedure. Irrigation of the third ventricle with warm saline was shown to produce polypnea and panting in the dog by Hammouda (1933). These observations are not altogether consistent but appear to indicate that a rising intracranial temperature is able to activate the heat loss mechanism.

In the course of a series of investigations in this laboratory of the rôle of the hypothalamus in the central regulation of body temperature (Ranson and Ingram, 1935; Teague and Ranson, 1936; Ranson, Fisher and Ingram, 1937; Ranson, Jr., 1938) it became desirable to reinvestigate the central action of heat in initiating heat loss activities and to attempt a more precise localization of the portion of the brain concerned.

METHODS

As a first step in this direction an apparatus was assembled which provided a high frequency alternating current, whose warming effect could be altered as desired by changing the voltage. The low power high-frequency unit consisted of a rectifier with an output of 600 volts at 50 ma., and a tuned-plate tuned-grid oscillator. A type 10 tube was used for the oscillator and its plate and grid tank circuits were calculated to oscillate at 1,000,000 cycles. The voltage across the electrodes was measured with a cathode ray oscillograph. It was convenient to measure voltages from peak to peak on the face of the tube and then divide by 2.8 to obtain the r.m.s. (root mean square) alternating current. Cats were used and the desired region of the brain was heated by passing the current between 2 electrodes or occasionally between 2 pairs of electrodes oriented within the brain with the aid of the Horsley-Clarke stereotaxic instrument. The electrodes, which consisted of straight lengths of 22 gauge nichrome wire, insulated with enamel to within 2 mm. of the exposed pointed tip, were fixed in a multiple needle carrier and inserted vertically through the dura after reflection of the skin and temporal muscles and removal of the appropriate portion of the calvarium. The location of the electrodes and the amount of damage done to the brain was checked in most of the experiments by the microscopical study of serial sections of the brains. Urethane in a dosage of 1 gm. per kilo, intraperitoneally, was the anesthetic employed and a consideration of the use of anesthetics in these experiments is presented elsewhere (Magoun, 1938). Whenever the initial polypneic panting which occurred in about one-third of the cases under urethane was present, ample time or fall in body temperature was allowed for its disappearance. We have considered the subsequent reactions to heating the brain in these animals valid, for the specificity of the nature and location of this stimulus was repeatedly demonstrated and extensively controlled by equally good or better results from other animals in which no such anesthetic effects were apparent.

In control experiments an iron-nichrome thermocouple, oriented in the posterior electrode carrier of the Horsley-Clarke instrument, was used to measure the temperature rise of the tissues around the electrodes during heating. The thermocouple tip was enameled in an attempt to prevent electrostatic pickup but Huntoon (1937) thinks this results in too high a reading. During our calibration of the apparatus with 11 and with 14.3 volts (r.m.s.) across the electrodes, it was found that 1 mm. laterally from the nearest electrode, the rises in brain temperature were 2.1° and 3.7°C. respectively and at 2 mm. laterally 0.7° and 1.2°C. Under the same conditions a thermocouple between the electrodes and 1 mm. from the nearest was raised 3.7° and 6.3°C. according to the voltage employed. These values indicate an increase in temperature of 75 per cent at 14.3 volts over that produced at 11 volts. After the current was turned on it took about one minute or more for the tissue to reach its highest temperature. At that time the rate of cooling

by the blood and conduction by the tissues equalled the rate of heat production. After current was turned off the tissue cooled rapidly at first and then more slowly to reach normal in about 2.5 to 3.5 minutes.

Since the rectal temperatures of the animals averaged 36.6°C., an increase of 3.7°C. caused by 11 volts would bring the region 1 mm. from the electrode to a temperature of about 40.5°, which is not destructively high. An increase of 6.3° caused by 14.3 volts (r.m.s.) would bring the temperature at 1 mm. from the electrode to about 43.0° which would account for the damage done to the brain tissue in some of these experiments. These calculations are based on the assumption that the temperature of the brain is normally about the same as that of the rectum. A study of our data in the light of the observation reported by Huntoon (1937) would indicate that our thermocouple readings were too high rather than too low.

Results

In a large series of experiments extensive exploration of the forebrain and midbrain of the cat revealed only a limited region of the brain from which responses to heating could be obtained. Local heating of this reactive area caused a marked acceleration of respiration, the excursion of which became very shallow. At a variable time after the increase in respiration began, the mouth was opened and rhythmic movements of the nostrils, angles of the mouth, and tongue appeared with each respiratory excursion. When at their peak these respiratory alterations constituted a characteristic "polypneic panting," and were frequently, but not invariably, accompanied by the appearance of sweat on the foot pads. The responses were in all points similar to those obtained by heating the entire animal.

The region of the brain from which these reactions were elicited on heating is schematically indicated on a paramedian sagittal section through the brain of the cat, shown in Fig. 1. The rostral portion of the reactive area is seen to be located in the ventrocaudal part of the telencephalon, between the anterior commissure dorsally and the optic chiasma ventrally. Its anterior limits extend a little farther forward than the preoptic area and the crossing of the anterior commissure. The responsive region is continued backward through the diencephalon in the dorsal part of the hypothalamus and the ventral part of the thalamus and at more caudal levels occupies a progressively more dorsal location. At the transition to the midbrain it is located in the vicinity of the central grey matter surrounding the anterior end of the cerebral aqueduct.

The rostral portion of the reactive region, which is cross-lined in Fig. 1. and which includes the preoptic area and the suprachiasmatic portion of the hypothalamus, has yielded better responses than the more caudal portion extending backward through the diencephalon. Heating this rostral region induced acceleration of respiration to an average rate of 255 excursions per minute. Panting appeared spontaneously and was marked and continuous throughout the responses. In many instances these pronounced respiratory alterations during heating were accompanied by the appearance of sweat on the foot pads.

In several respects the responses to heating the reactive region through the diencephalon, enclosed in dotted lines in Fig. 1. were weaker than those

just considered. The responses from the diencephalon were less abrupt in onset, required a longer time to reach their peak and were quantitatively smaller, the average polypnea amounting only to 155 excursions per minute. In addition, the panting associated with the responses from the diencephalon only persisted for brief periods and usually required the facilitation provided by holding the mouth open (Lilienthal and Otenasek, 1937) to appear at all.

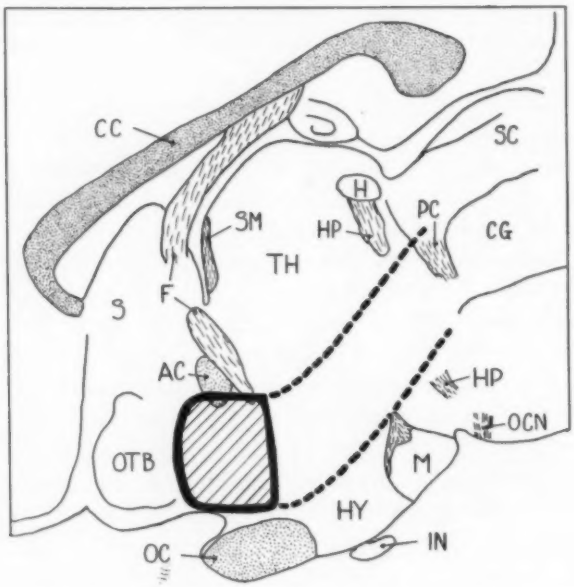

FIG. 1. Schematic outline of the region reactive to heating, projected on a paramedian sagittal section through the brain of the cat. Abbreviations for all figures are as follows:

AC	anterior commissure	HY	hypothalamus	OCN	oculomotor nerve
BP	basis pedunculi	IC	internal capsule	OT	optic tract
C	caudate nucleus	IN	infundibulum	OTB	olfactory tubercle
CC	corpus callosum	LV	lateral ventricle	PC	posterior commissure
CG	central grey matter	M	mammillary body	S	septum
E	entopeduncular nucleus	MB	midbrain	SC	superior colliculus
F	fornix	MFB	medial forebrain bundle	SM	stria medullaris
GP	globus pallidus	MT	mammillo-thalamic tract	TH	thalamus
H	habenula	OC	optic chiasma	3V	third ventricle
HP	habenulo - peduncular tract				

The difference in reactivity, in our opinion, indicates a reduced concentration of reactive elements in the responsive field through the diencephalon.

It has been mentioned that the reactive region shown in Fig. 1 is the only portion of the brain studied which responds to local heating and this statement is based upon the negative results obtained to heating at locations distributed through a large portion of the cerebral cortex, the subcortical white matter, the ventral telencephalon rostral to the reactive area, the

caudate and lentiform nuclei of the corpus striatum, the diencephalon surrounding the responsive field and the midbrain behind it as far caudad as the anterior end of the pons. The absence of response from these negative regions was checked by heating at varying positions out to 8 mm. lateral from the midline and at varying dorsoventral locations extending from the dorsal surface of the cerebral hemispheres to the base of the brain. In such exploration the negative results elsewhere were validated by characteristic responses obtained from the reactive region shown in Fig. 1 at the beginning and end of the experiments.

With this introduction, a series of representative protocols may be presented in which the region between and around two electrodes inserted 2 mm. to either side of the midline was heated at succeeding dorsoventral locations in 6 transverse planes extending in serial order from a level just in front of the anterior commissure through the diencephalon to the anterior end of the midbrain, *i.e.*, through the area of distribution of the reactive field shown in Fig. 1. The location of the electrodes and the respiratory responses to heating in each of these protocols are illustrated in Figs. 2–7.

PROTOCOLS

Protocol 1 (*Cat 1, Fig. 2*). The first protocol illustrates the responses to heating at a level ½ mm. rostral to the crossing of the anterior commissure and extending ventrally through the anterior tip of the optic chiasma. Positions a, b, c, d in Fig. 2A show the location of the electrodes during each period of heating and the respective reactions obtained are charted in Fig. 2B. The absence of response to heating at location a, obviously indicates that this region was negative and such negative locations need not be commented

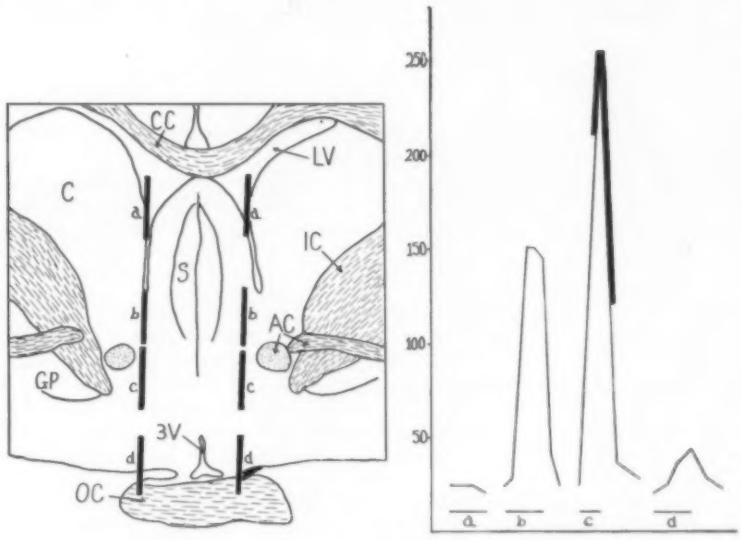

FIG. 2A. Transverse section through the brain of Cat 1. The positions of the two electrodes during heating are shown at a, b, c, and d.

FIG. 2B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c and d, Fig. 2A. The rate of respiration is shown on the ordinate; panting is shown by a heavy line. Period a represents 5 min., other times are in proportion.

upon further. It can be seen that heating at position c, Fig. 2A, at a vertical level corresponding to that of the anterior commissure and the region ventral to it, induced (response c, Fig. 2B) an increase in respiratory rate from 25 to 252/min. with panting (heavy line in chart). A considerably weaker response (b, Fig. 2B) was obtained on heating at position b, dorsal to the location of the anterior commissure and wherever in these experiments a weak reaction was obtained from a location immediately above or below that yielding a good response, we have been inclined to consider the possibility of spread of heat to the closely adjacent more reactive region. It should be noted that heating at position d, where the meninges at the base of the brain were undoubtedly warmed was almost negative (d, Fig. 2B), and the responsive region is clearly seen to lie within the brain. This has been repeatedly verified in many experiments.

Protocol 2 (*Cat 2, Fig. 3*). The second protocol illustrates the response to heating at the level of the crossing of the anterior commissure. The location of the electrodes is shown in Fig. 3A, and the responses to heating are charted in Fig. 3B. Heating at location d, for

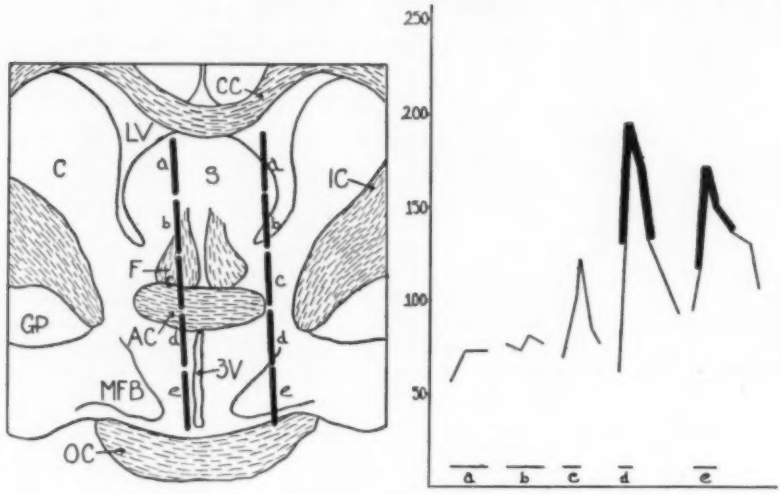

FIG. 3A. Transverse section through brain of Cat 2. The positions of the two electrodes during heating are shown at a, b, c, d and e.

FIG. 3B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 3A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 5 min., other times are in proprotion.

the most part ventral to the anterior commissure, produced (response d, Fig. 3B) an increase in respiration from 60 to 192/min. with panting. Heating at location c immediately dorsal to that just described, yielded a much weaker response (c, Fig. 3B), and at location e, immediately ventral to it a slightly weaker reaction with increase of respiration to 168/min. and panting (e, Fig. 3B). The best response (d, Fig. 3B) was somewhat weaker than those usually obtained from this region which may have been due either to the brief period of heating or to the asymmetrical position of the electrodes with reference to the midline (Fig. 3A).

Protocol 3 (*Cat 3, Fig. 4*). The third protocol illustrates a response to heating the suprachiasmatic hypothalamus at a level ½ mm. caudal to the crossing of the anterior commissure. The position of the electrodes is shown in Fig. 4A and heating produced an increase in respiratory rate from 36 to 288/min. with panting (Fig. 4B). Unfortunately other dorsoventral locations were not heated in this animal but the marked response obtained from this position indicates that it lies at or very close to the responsive center.

Protocol 4 (*Cat 4, Fig. 5*). The fourth protocol illustrates the responses obtained at a level through the anterior thalamic nuclei above and through the infundibulum below.

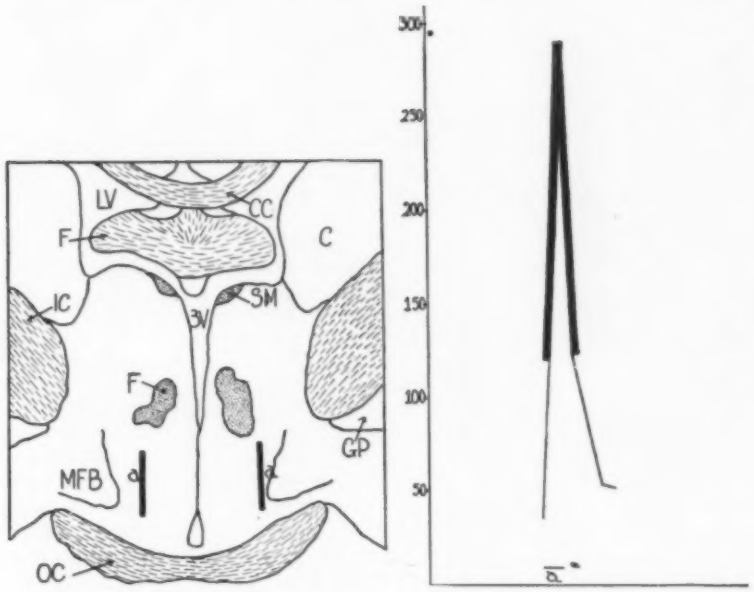

FIG. 4A. Transverse section through the brain of Cat 3. The position of the two electrodes during heating is shown at a.

FIG. 4B. Chart showing the respiratory response obtained from heating at position a, Fig. 4A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 2½ min.

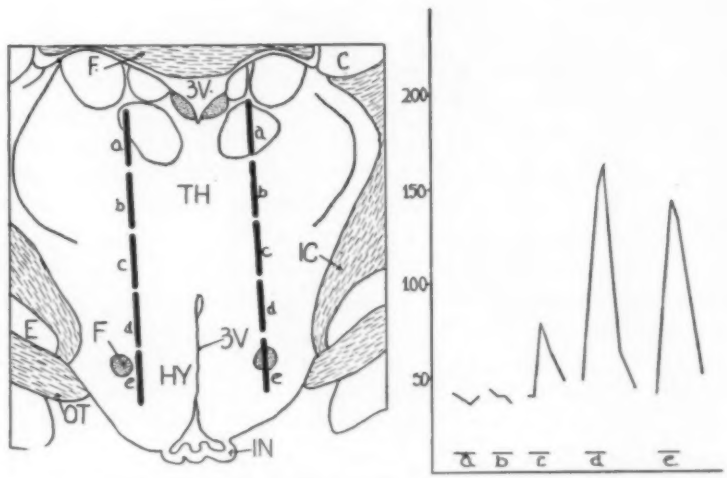

FIG. 5A. Transverse section through the brain of Cat 4. The positions of the two electrodes during heating are shown at a, b, c, d and e.

FIG. 5B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 5A. The rate of respiration is indicated on the ordinate. Period a represents 3 min.; other times are in proportion.

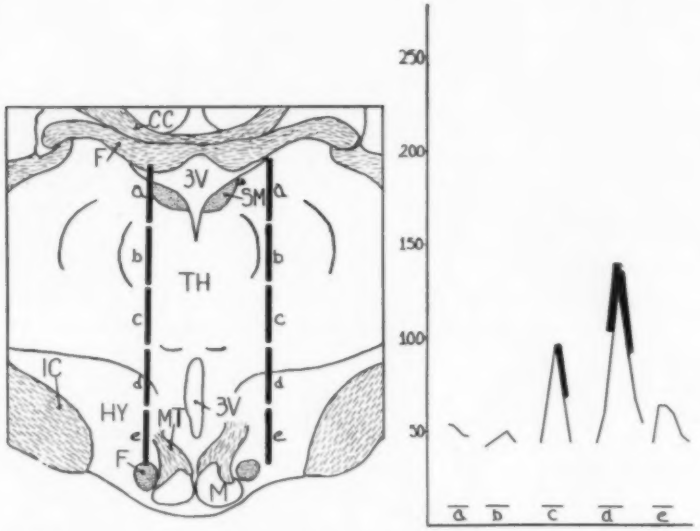

FIG. 6A. Transverse section through brain of Cat 5. The positions of the two electrodes during heating are shown at a, b, c, d and e.

FIG. 6B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 6A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 3 min.; other times are in proportion.

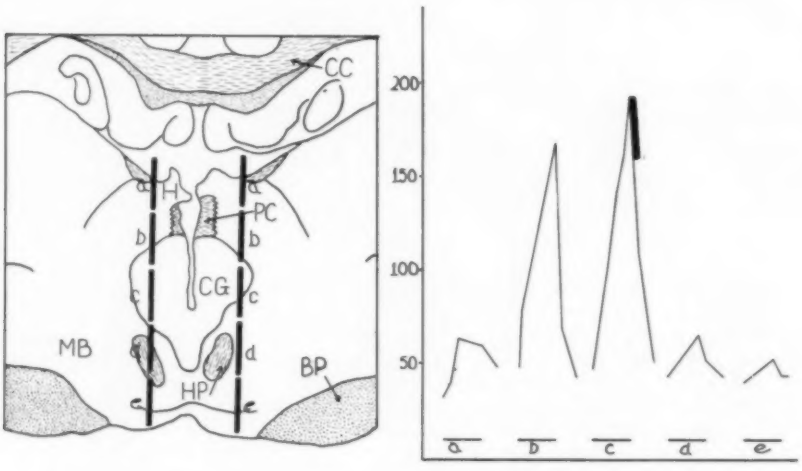

FIG. 7A. Transverse section through the brain of Cat. 6. The position of the electrodes during heating is shown at a, b, c, d, and e.

FIG. 7B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 7A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 5 min.; other times are in proportion.

Heating at location d produced an increase in respiratory rate from 48 to 164/min. without panting (d, Fig. 5B). Heating at location e produced an increase in the rate of respiration from 40 to 144/min. (e, Fig. 5B) and though there was no spontaneous panting the animal panted for a brief period when the mouth was held open.

Protocol 5 (*Cat 5, Fig. 6*). The fifth protocol illustrates the reactions to heating at a level through the nucleus medialis dorsalis of the thalamus above and through the mammillary bodies below. Heating at location c produced an increase in respiratory rate from 44 to 96/min. with panting (c, Fig. 6B). Heating at location d produced an increase in the rate of respiration from 44 to 138/min. with panting (d, Fig. 6B). Heating at location e produced a slight increase in respiration from 44 to 64/min.

Protocol 6 (*Cat 6, Fig. 7*). The sixth protocol illustrates the responses to heating at a level through the caudal tip of the habenulae and the rostral fibers of the posterior commissure above, and through the rostral portion of the midbrain ½ mm. behind the mammillary bodies, below. The best response was obtained from location c where heating produced an increase in respiratory rate from 48 to 192/min. with a short period of slight spontaneous panting (c, Fig. 7B). Stronger heating at location b immediately dorsal to that just considered gave a slightly weaker response, the respiratory rate increasing to 168/min. (b, Fig. 7B). The responses to heating this transition region from diencephalon to midbrain were somewhat more marked than those elicited from more rostral regions of the diencephalon in other animals. This may be accounted for either on the basis of the variation present in different experiments or by the supposition of a concentration of reactive elements in the transition region from diencephalon to mid-brain comparable to that more evidently present in the ventral part of the telencephalon.

The results which have just been described have been presented first to provide an initial survey of the nature of the reactions and the location of the responsive region to heating the brain. Additional information on several points may now be presented.

Lateral limits of responsive area. The responses obtained to heating between and around electrodes situated 2 mm. to either side of the midline in the experiments just described and many others imply a medial location of the reactive region and this is supported by the results from an experiment in which two electrodes were inserted almost in the midline, one in the preoptic region and the other behind it in the anterior hypothalamus. Heating the midline region between the electrodes induced an increase in respiratory rate from 48 to 240/min. with panting, *i.e.*, a marked response.

A large amount of negative data was accumulated to heating between electrodes situated 4 and 8 mm. lateral to the midline, and it is safe to conclude that the responsive elements are concentrated within 4 mm. of either side of the midsagittal plane. There are many indications that the lateral limits of this concentration may be still more medially placed. The schematic outline of the reactive field shown in Fig. 1 is projected on a sagittal plane 1 mm. lateral to the midline, but only to indicate in a general way its medial location.

Time relations of responses. In a large number of marked reactions from the ventral telencephalon, the acceleration of respiratory rate began between ½ and 1½ min. after the onset of heating. Since 1 min. or more was required after the onset of heating for the tissues to reach their highest temperature (see Methods), the actual latent period of the reaction was probably very brief. Once begun the increase in respiratory rate was fairly abrupt and the peak rate was reached between 1 and 4 min., usually between 2 and 3 min.

after the onset of heating. Panting began 1 to 2½ min. after the onset of heating, at respiratory rates ranging between 80 and 210/min. When sweating was present it was usually observed between 1½ and 2 min. after the onset of heating.

When heating was discontinued the respiratory rate fell at first abruptly and then more slowly until the original basal rate or one slightly higher was reached after 1½ to 6 min., usually after 2 to 4 min. Panting stopped between ½ and 2 min. after the cessation of heating at respiratory rates ranging from 120 to 150/min. The time required for deceleration of respiration and cessation of panting after heating was discontinued, corresponded closely to that required for the tissues to cool (see Methods).

Repetition of heating. In each of several animals the rostral portion of the reactive region was repeatedly heated between two pairs of electrodes with results confirmatory of those already presented. The results from one experiment (Cat 7) are illustrated in Fig. 8. One pair of electrodes was inserted in a plane through the crossing of the anterior commissure and another pair in a plane through the infundibulum (Fig. 8A). The preoptic region and anterior hypothalamus enclosed between the electrodes was repeatedly heated with the results shown in Fig. 8B.

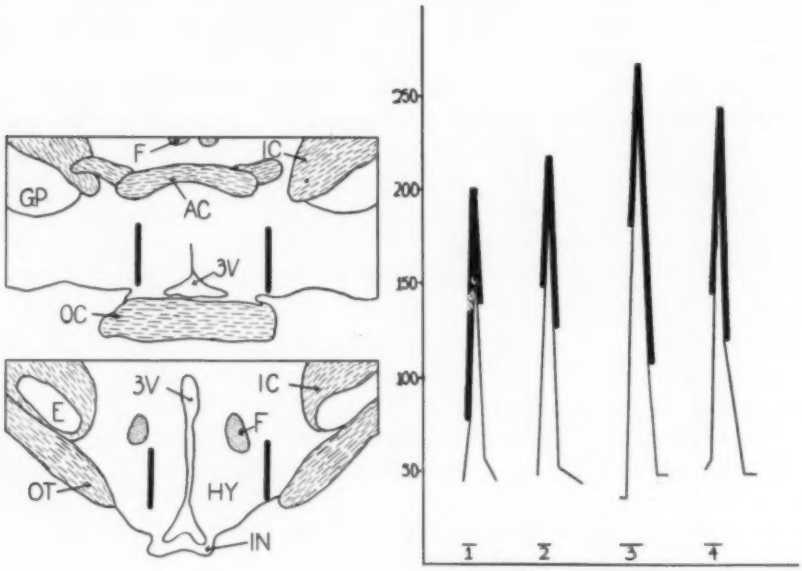

FIG. 8A. Two transverse sections through the brain of Cat. 7. The position of the the rostral pair of electrodes during heating is shown in the upper section, that of the caudal pair is shown in the lower section.

FIG. 8B. Chart showing the respiratory responses obtained to repeated heating of the region between the electrodes shown in Fig. 8A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period 1 represents 1½ min.; other times are in proportion.

Initial heating for 1½ min. induced an increase in respiratory rate from 44 to 198/min. with panting (response 1, Fig. 8B). After a 15 min. interval a second period of heating for 1½ min. induced an increase in the rate of respiration from 48 to 216/min. with panting and the appearance of sweat on the footpads (response 2, Fig. 8B). Following another 15 min. interval, a third period of heating for 3 min. induced an increase in respiratory rate from 36 to 264/min. with panting and the appearance of sweat on the footpads (response 3, Fig. 8B). Following a 20 min. interval, a fourth period of heating for 2 min. induced an increase in the rate of respiration from 48 to 240 /min. with panting (response 4, Fig. 8B). Information on repetition of responses was usually gained in experiments in which the region of the brain between two pairs of electrodes was heated because such experiments were not appropriate for the study of detailed localization. The responses to heating the region of the brain between a single pair of electrodes could be repeated just as satisfactorily, however.

Distinction between effects of faradic stimulation and heating. In the intervals between heating in the experiment just described and in several others, the effect of faradic stimulation of the region of the brain between the electrodes was observed. This regularly led to sympathetic discharge, due to excitation of hypothalamus, causing maximal dilatation of the pupils, maximal retraction of the nictitating membranes, erection of the hair on the back and sometimes occasioned struggling. Respiration was accelerated, sometimes after an initial apnea, respiratory excursions were deep and labored and occasionally were associated with facio-vocal activity as in other experiments (Kabat, 1936; Magoun, Atlas, Ingersoll and Ranson, 1937). In one instance faradic stimulation produced panting and we have occasionally observed panting in response to faradic stimulation of the anterior hypothalamus in other experiments.

In contrast to this indiscriminate action of faradic stimulation which excited everything within range, the effect of heating was specific and precise, leading only to the excitation of heat loss mechanisms. During the responses to heating, the pupils and nictitating membranes remained unchanged and there was no erection of hair or struggling.

Body temperature. The rectal temperature at which a group of 25 marked responses to heating the ventral telencephalon were obtained in these experiments ranged from 35.0 to 38.4°C. The larger number (19) of these responses was elicited at rectal temperatures between 35.5 and 37.5°C., which are subnormal and demonstrate that an elevated body temperature is not essential for the initiation of heat loss activity when the appropriate region of the brain is adequately heated.

Heat loss activities were not maintained for a long enough time in any of these experiments to produce a clearcut depression in body temperature beyond the gradual fall which took place in each instance as a result of the anesthesia.

Effect on the brain. A histological study was made of the brains of most of the animals used in this investigation and permitted the determination of any damage done to the brain by heating. A voltage of 11 was employed in heating the responsive region in the ventral telencephalon in a total of 9 instances with no damage to the brain. In heating this region, 14.3 volts were employed in 11 instances without damage or with only very slight damage in the immediate vicinity of the electrodes. In 9 other instances heating the ventral telencephalon with 14.3 volts resulted in moderate to marked damage of the brain around and between the electrodes.

A voltage of 11 was employed in heating the responsive region in the diencephalon in one instance with no damage to the brain. In heating this region 14.3 volts were used in three instances with slight damage to the brain in the immediate vicinity of the electrodes. In five instances heating the diencephalon with 14.3 volts caused moderate to marked damage of the brain around and between the electrodes. In both the telencephalon and diencephalon the usual responses were obtained in the instances when the brain was damaged and presumably were elicited from the adjacent reactive region outside the area of damage.

In a number of preliminary experiments in this series excessive heating (28.6 volts) of the area rostral or dorsal to the reactive region shown in Fig. 1 produced the usual responses. These responses could not have been obtained from the area in the vicinity of the electrodes, however, for in such instances this area was widely destroyed by the excessive heat employed. In our opinion, such reactions were obtained from spread of heat to the responsive region shown in Fig. 1. In all instances when damage occurred the responses subsided just as rapidly following cessation of heating as when no damage was present. The experiments in which the brain was damaged provide little evidence for localization and throughout this presentation the emphasis has been placed on those results which were obtained with a minimum amount of heating and with little or no injury to the brain.

Discussion

It may be noted that the region in the ventral telencephalon responsive to heating, overlaps to some extent the ventral and caudal distribution of what is probably a descending cortical pathway for respiratory inhibition, yielding a decrease in respiratory rate and amplitude when activated by localized faradic stimulation (Kabat, 1936). The appearance of polypneic panting in acutely decorticate animals has recently been attributed by Lilienthal and Otenasek (1937) to release from cortical inhibition through destruction of such a pathway. Lest the same explanation suggest itself for the responses to local heating of the reactive region delimited in these experiments, it may be emphasized that these responses to heating were not dependent upon such destruction, for the larger number of reactions were obtained without appreciable injury to the brain. Furthermore, had these responses been dependent upon destruction, they should have continued

indefinitely instead of disappearing as they did with the cessation of heating. Repetition of the responses should have been impossible, yet they could be repeated apparently indefinitely.

To us the obvious interpretation of these results is that in these experiments we have been setting into play by artificial heating the same mechanisms in the same regions of the brain which are activated in the normal animal when the temperature of the blood rises above normal. Such an interpretation provides a logical explanation of the results obtained in a study of the effect of lesions in this region which, as has been shown by Teague and Ranson (1936) and by Clark, Magoun and Ranson (in preparation), abolish the animal's ability to regulate effectively against high environmental temperatures. Further consideration of the results of these experiments from the point of view of the central regulation of body temperature will be presented elsewhere (Clark, Magoun and Ranson, in preparation).

The results of these experiments should not be taken to indicate that the region responsive to heating contains the final efferent collection of supranuclear neurons for coordinated polypneic panting, for this may still be obtained after the area here delimited has been largely (Lilienthal and Otenasek, 1937) or entirely (Keller, 1933) destroyed. The responsive area to heating found in these experiments may contain afferent-like elements capable of exciting efferent groups of neurons situated at more caudal levels.

Summary

Local heating of the brain of the cat with low voltage, high frequency current passing between electrodes oriented with the Horsley-Clarke apparatus has demonstrated a reactive region which responds to heating by marked acceleration of respiratory rate, panting and in some instances by the appearance of sweat on the foot pads.

The reactive elements appear to be concentrated in the medial portion of the caudal part of the ventral telencephalon and, in lesser concentration, are continued backward through the diencephalon as far as the anterior end of the midbrain. In the telencephalon the responsive region occupies a position between the anterior commissure and the base of the brain. Through the diencephalon it is located in the dorsal part of the hypothalamus and the ventral part of the thalamus, and occupies a progressively more dorsal position at more caudal levels. At the anterior end of the midbrain it is located in the vicinity of the central gray matter surrounding the transition from third ventricle to cerebral aqueduct.

The results are interpreted as indicating that the reactive region contains structures which are activated by the rising temperature of the blood and lead to heat loss activity in the normal animal when overheated.

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LOCALIZED THERMAL CHANGES IN THE CAT'S BRAIN*

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THE Horsley-Clark instrument has been used in this laboratory for the study of local electrical (Gerard, Marshall and Saul, 1936) and metabolic (Brookens, Ectors and Gerard, 1936) activity in known anatomical structures in the brain. It seemed probable that temperature could be successfully studied with the same apparatus carrying a thermojunction, and information thus be obtained on the energy liberation of active nerve cells, the vasomotor concomitants of activity, or both.

Heat production of the isolated frog spinal cord, under direct or reflex activation, has been studied by several workers, and the most complete evidence (Holzlöhner and Trurnit, 1937) indicates a reasonable parallelism to peripheral nerve. A total heat up to 10^{-3} cal./gm. is liberated during 5 to 12 minutes (18°C.) following one second of stimulation with 80 induction shocks per second applied at the end of the cord away from the thermopile. Of this, about 3 per cent is initial heat, and the remainder recovery heat plus any due to repetitive discharges. This active heat production is about twice the resting heat rate, 5×10^{-4} cal./gm./sec., as estimated from respiration data (Rosenberg, 1935; Batz, 1923). For the frog sciatic, equivalent values are 8×10^{-6} cal. initial heat, 5×10^{-5} cal. total—duration 30 minutes, at 20°C.—per second of stimulation at maximal activity (see Feng, 1936). Per single impulse, the initial heat is 7×10^{-8} cal. gm., total 2×10^{-6}. In the non-medullated leg nerve of the spider crab at maximal stimulation, initial heat per gm./sec. is about 10 times that of frog nerve under similar conditions, and total heat is 18 or more times as great. In terms of maximal evoked activity, then, the total heat produced by the frog spinal cord is well over 20 times that of the sciatic nerve. If comparisons are made at lower frequencies of stimulation (*e.g.*, 8/sec.) the ratio is much higher, up to 100 times—possibly because of repetitive discharges by the central units.

Two other factors must, however, be considered, both of which would tend to multiply the true difference between cells and fibers. 1. In nerve, a maximal stimulus activates all the units; while stimulation of the lumbar cord—presumably of ascending motor paths—engages only a fraction of the neurons and may inhibit the activity of many. 2. In nerve, the neural elements compose one to two-thirds of the total mass; in brain, possibly as little as 1 per cent. The energy per unit of mass per single activation may, therefore, be several hundred times as great in a nerve cell as in its axon.

On turning to the mammalian brain *in situ*, a further temperature difference appears, as well as the complication of a circulation. No work to date measures the true heat production of activity, and even the increased oxygen

* A preliminary report of this work appeared in the *Amer. J. Physiol.*, 1936, *115:* 59.

consumption of active brain is highly uncertain. Resting respiration rates are rather more dependable—some 5000 cmm./gm./hr. for cat cortex at the moment of removal (Brookens, Ectors, and Gerard, 1936 and unpublished; Schmidt, 1928), against 180 for dog nerve, also at 37°C.—and if the increase on activity is proportional, brain heat is about 30 times that of nerve, per equal gross mass; or 1.5×10^{-3} to 4.5×10^{-3} cal./gm./sec. (depending on whether a 100 or 300 per cent increase is assumed for activity). One might anticipate, then, a heat production of the order of 6×10^{-5} cal. per impulse in an active portion of the brain; and if the rather arbitrary figure of 50 discharges per second be assumed for activity evoked by sensory stimulation (at least electrical discharges well over this frequency do occur) brain temperature would ultimately rise at the rate of 0.003°C./sec., aside from heat loss. This same value for maximal active heat production is obtained by doubling the resting level; a relation seen to hold also for frog cord and, except under special conditions, for frog nerve.

Heat loss, however, is continuous; partly by conduction and radiation through the skull or from the exposed brain surface, mainly through the blood stream. The actual temperature change in a region of the brain, associated with its activity, will be a balance between the extra heat produced—depending on degree of excitation, concentration of active cells, absolute heat production, duration of total heat, etc.,—and the extra heat lost—depending on blood-brain temperature difference, richness of vascular bed, volume of blood passing, etc. Blood flow is, of course, the important variable; and a vasodilatation accompanying activity might well overshadow an increased heat production so that brain temperature is actually lowered.

To some extent it has been possible to disentangle these several factors, as will be discussed, but fortunately the cause of thermal changes is irrelevant to one important aspect of our study—evidence of local alterations in individual sensory systems when these are stimulated via appropriate receptors.

Renewed extensive studies of the control of brain circulation (see Wolff, 1936, for recent summary) have utilized, among others, thermal methods for measuring flow. In Gibbs' (1933) arrangement, the thermojunctions are continually warmed above blood temperature and an increased blood flow has a consequent cooling effect; in Schmidt and Pierson's (1934) the junctions are cooled and increased flow warms them. Steep temperature gradients are maintained, with several degrees difference between needle and blood, so that any true neural heat production would not be seen. In the recent work of Feitelberg and Lampl (1935), however, using one thermojunction in the brain and the other in the carotid artery, the small temperature difference may well include true neuron heat; and in many respects our results are in agreement with theirs.

Methods

A thermoneedle, 20 gauge hypodermic needle with a single junction of 38 gauge constantin and enamelled copper wires insulated with bakelite varnish, was arranged to fit on a brass rod clamped in the carriage of the Horsley-Clark instrument. The wires, in separate rubber tubing, ran 75 cm. to the constant temperature junction, embedded in

a brass block and kept in an ice and water mixture. For certain experiments the second junction, also in a needle, was inserted in a blood vessel or the abdomen. The entire circuit, including a potential divider, series and shunt resistances, and a Moll Zd galvanometer, was of copper with fixed connections. A variable and reversible balancing potential was thrown into the fixed divider in the usual manner.

The resistance of the thermal elements, 43 ohms, was about that of the galvanometer, 30 ohms. The sensitivity, by calculation and by direct calibration, was 1 mm. deflection (scale at 1.25 m.) = 0.00075°C. (in some experiments 1 mm. = 0.001°C.). With additional series and shunt resistances in, a less sensitive combination, 1 mm. = 0.003°C., was used for preliminary orientation or to follow larger temperature changes. Movements of the galvanometer spot were followed manually with a rack and pinion stylus activating a writing point on a kymograph, and continuous records obtained.

Experiments were performed on 35 cats and 3 dogs under nembutal (35 mgms./kilo., intraperitoneally) or basal nembutal (25 mgm./kilo.) supplemented with ether. The Horley-Clark instrument was attached as usual and set at the desired A-P and R-L coordinates. A small skin incision was made at the indicated position and the skull drilled (1 mm. hole) to admit the needle. Before or after placing the thermojunction, a concentric electrode was usually inserted to the same depth and action potentials in response to optic or somaesthetic stimulation observed, thus insuring that temperature observations were made in the desired sensory pathway. A light shining into the eyes for ½ to 2 minutes, squeezing and manipulating the toes of the contralateral forepaw over similar periods, and ammonia vapor blown into the nostrils constituted the stimuli used.

Results

Anaesthetic effect. Brain temperature falls rapidly under the influence of an anaesthetic or narcotic drug. The amount of fall can be estimated only from animals with indwelling thermocouples, since in acute experiments a change has already occurred when observations begin. Even so, after intraperitoneal nembutal and the 30 to 40 minutes required to place the instrument, the brain cools a further 1.2 to 1.5° during another 2 to 4 hours. In the chronic animal the total fall for a similar dose is 2.5–3°C. The rate of cooling tapers off progressively until a temperature plateau is reached. This is then maintained for 15 to 30 minutes and passes over into a rise. Another nembutal injection promptly reestablishes the falling base line, which again, finally, turns upwards. Metrazol, a stimulant, conversely, sends the temperature up. Ether inhalation during the rising base line initiates a prompt but brief rise in brain temperature, some 0.05°C. within a minute or two, and then an even more precipitate fall to still lower values. By controlling ether administration after the nembutal fall has turned into a rise it is possible to hold the brain temperature fairly steady for hours—and most other observations were made against such a base line (Fig. 1). It is important to keep in mind that all vasomotor and other responses are obtained from a narcotized, and therefore depressed, brain.

The thermal changes in the brain are not a passive consequence of cooling of the entire body—due to muscular relaxation, cutaneous dilatation, and the like—for entirely similar changes in the brain are recorded when the "neutral" junction is placed in the abdomen or the aorta instead of in the usual constant temperature mixture. These drugs, therefore, depress brain temperature relative to that of the blood: indeed the temperature difference between them, in favor of the brain, may actually reverse under sufficient

narcosis. This probably accounts for the immediate warming produced by ether—a rapid vasodilatation temporarily masks the diminished brain heat.

Brain temperature diminishes under depressant drugs because its intrinsic heat production is lowered. Studies of oxygen utilization from circulating blood, indicate that this is decreased to one-third (Hou, 1926) or even one-tenth (Gayda, 1914) under anaesthesia. Changes in blood flow and temperature are, of course, additional factors (see below), but we are satisfied that the metabolic level of brain cells is most directly concerned. There is a close parallel, for example, between the temperature curve and depth of anaesthesia. As the brain begins to warm up the animal becomes more responsive to stimuli, may move spontaneously, and starts to "come out" of anaesthesia. Conversely, considerable sensory stimulation may initiate or accelerate the temperature rise.

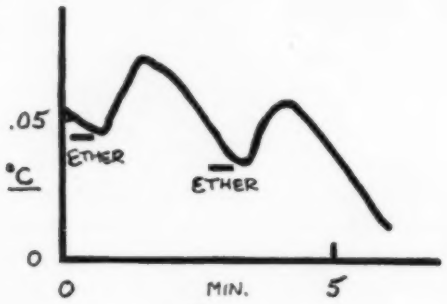

FIG. 1.

Aside from any interpretation, the brain temperature curve seems to offer an extremely sensitive and accurate index of the course of anaesthesia. It promises to measure the intensity, time-course, and locus of anaesthetic action, and experiments along these lines are in progress.

Temperature gradients in the brain. The only way in which it is physically possible for the brain to remain cooler than the blood is for heat loss from the head, by other routes than the blood stream, to exceed its local production. Over short time intervals, before equilibrium is established, warming the blood or cooling the brain will of course invert the usual relation; but at equilibrium, unless some other route of heat dissipation exists, this cannot remain the case. So long as any heat is developed in an organ, the blood must warm up in passing through it, for even when metabolism is fully in abeyance the tissue temperature will still be passively held at that of the blood circulating it—unless another route of heat loss exists. For the limbs, surface conduction and radiation constitute an impressive means of heat loss—the venous blood from a leg may be 0.1°C. cooler than the arterial, and be warmed 0.1° by placing a 60 watt lamp above the leg—and a similar situation, though less pronounced, might be anticipated for the head.

Actually a very definite temperature gradient exists within the brain, central regions being warmer than more surface ones by as much as 1.4°C. As a

thermoneedle is pushed from one parietal region to the other, temperature regularly rises and then falls. A similar rise occurs on penetrating from the vertex, sometimes ending with slight fall at the base (Fig. 2). The regularity of the change precludes its dependence on any particular structural pattern; and its symmetry about the midline eliminates any artificial cooling due to the small skull opening for introducing the needle. (A false gradient due to conduction of heat outwards along the shank of the hypodermic needle is excluded by this reversal of the gradient on crossing the midline; but as an extra check the needle sheath was withdrawn after placing the fine wire thermocouple and the same temperature gradient still appeared as this was later removed.)

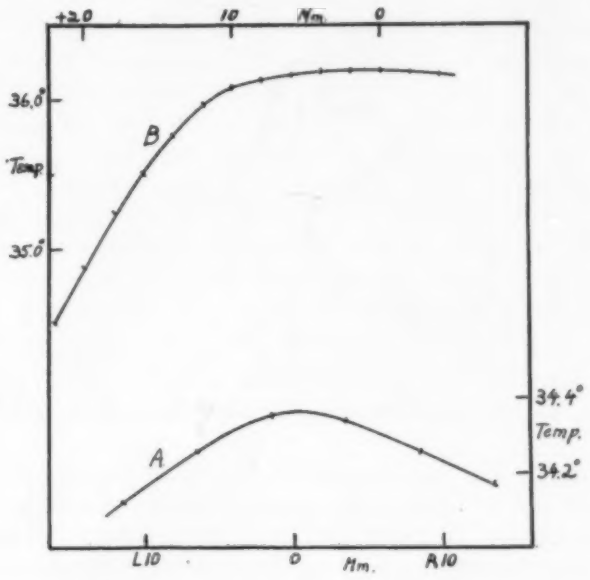

FIG. 2 A. Temperature curve in horizontal plane from left parietal cortex to right. B. Same in vertical plane from cortex to basal skull. Abscissa—Horsley-Clark instrument setting.

Clearly, then, the brain is continually cooled by heat loss through the skull and scalp; and possibly human hair has more than an aesthetic value, in helping to maintain brain temperature. That heat easily penetrates this vascular barrier, is shown by the considerable cooling of the brain that results from applying an ice bag to the head.

Brain-blood temperature differences. In unanaesthetized animals, Feitelberg and Lampl (1935) found the motor cortex as much as 0.4°C. warmer than the carotid blood. Under paraldehyde, the brain temperature fell to 0.3°C. below that of the blood stream. We have never observed such great temperature differences, but also find the brain to be warmer or cooler than the carotid blood, depending on anaesthetic level and degree of operative expo-

sure. The same is true for longitudinal sinus blood compared to that in the carotid. Extreme differences were, carotid 0.037°C. warmer to 0.004°C. cooler than sinus; brain 0.034°C. warmer to 0.001°C. cooler than carotid. When arterial blood and brain are at the same temperature, any rapid temperature change recorded from the brain cannot be due to vasomotor changes.

When the blood is warmer, a vasodilatation would cause a rise in brain temperature; when cooler, a fall. The former situation is deliberately induced by Schmidt and Pierson's (1934) cooled needle technique, the latter by Gibbs' (1935) heated needle one. By comparing the brain temperature change induced by a given stimulus under these various thermal relations it is possible to discriminate between the effect of vasodilatation and that of increased neural heat production. A control in point is the warming up of leg muscles, initially above arterial blood temperature, on stimulating the sciatic nerve.

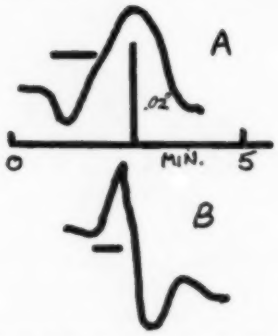

FIG. 3 A. Carotid occluded during signal. B. Same, but needle heated.

Other controls. At first the fine copper and constantin wires of the thermocouple were soldered to larger wires of the same metals where they emerged from the needle shank. It was found that temperature changes here set up potentials, presumably due to slight differences in composition, and later the fine constantin wire was continued to the cold junction and the fine copper ones to fixed copper connections in the permanent circuit which were well shielded from sudden temperature change.

The eyes were illuminated by a flash light or a 60 watt bulb. In the latter case a slow warming of the brain occurs over minutes; in the former, no direct heating action could be detected. In all the positive optic experiments such extraneous warming was excluded by controls with the eyes covered or with the thermojunction in non-optic regions.

The paw stimulation, when very vigorous, was found to cause a general blood pressure rise of 5 to 10 mm. Hg. as a maximum. The rise appeared promptly at the start and vanished as promptly at the close of the period of actual stimulation. No pressure change accompanied optic stimulation. A change in brain blood flow secondary to non-specific systemic effects is thus excluded as a cause of the localized thermal changes elicited by these stimuli.

Carbon dioxide excess and oxygen deficiency lead to vasodilatation in the

brain. During CO_2 inhalation and following a period of carotid occlusion, brain temperature rose (fell during occlusion). With the needle heated some 2°C., the same procedures caused a temperature fall (rise during occlusion). (Fig. 3) Clearly arterial blood was warmer than the brain in the first test, cooler than the heated brain and needle in the second, and the thermal changes were due to vasodilatation.

Specific Responses

Optic. With the thermocouple in optic pathways—lateral geniculate, radiations, or visual cortex—shining light in the eyes leads to a rise in temperature; other brain regions are negative. The rise is variable in duration, magnitude and form, depending on partially unknown variables; but in a sequence of tests made under essentially constant conditions there is good reproducibility. Fig. 4 shows the average of 35 positive experiments. The temperature rise begins 30–60 sec. after a 60 sec. period of illumination, reaches a maximum of 0.015°C. in 120 sec. and is over in 300–360 sec. Sometimes a secondary hump appears on the descending limb. In three experiments, light evoked a similar appearing temperature fall; and in 2 others a fall during stimulation preceded a rise following. These cases of heat loss must be due to vasodilatation and greater flow of blood that is cooler than the brain. The rise of temperature, however, cannot be similarly accounted for by increased flow of warmer blood, for in no case was a rise converted into a fall by heating the needle tip. The rise is, therefore, a consequence of increased heat production by the active neurons, though unquestionably modified by an increased blood flow when the brain is not at blood temperature.

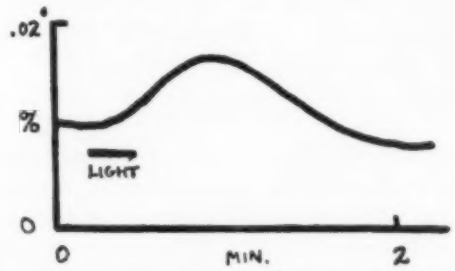

Fig. 4. Average curve from lateral geniculate body (A8, L8, +3.5) on illuminating eyes.

Somaesthetic. Stroking, pinching, and kneading the paw of the contralateral (mainly) fore leg causes a temperature rise in cutaneous radiations and cortex. The localization has been much less rigid than in the optic experiments, however, and occasionally quite generalized responses were obtained. Some characteristic records are reproduced in Fig. 5. While similar to the optic curves, these show a shorter latent period and more frequently begin with a negative dip. Further, it has proved possible to invert a heat curve resulting from paw stimulation by heating the needle tip. We conclude that

the major effect in this case is vasodilatation, though some increase in heat production is not excluded. Since most records of this series were made from tracts, nerve fibers with low metabolic intensity, and most optic ones from nuclei, cells and their connections with an intense metabolism, the differences are understandable.

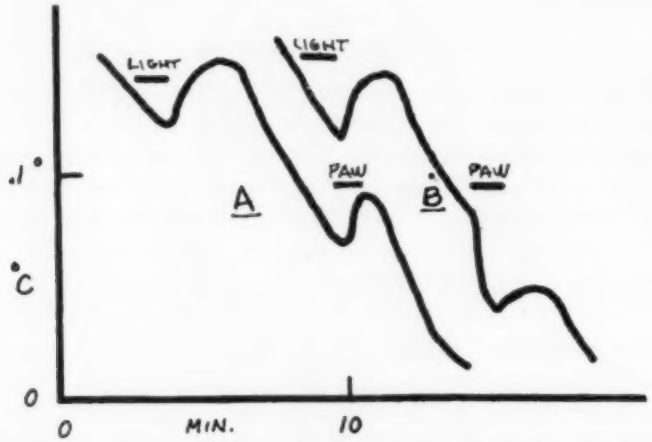

FIG. 5 A. Single responses to optic and to somaesthetic stimulation. B. Same, but needle heated. Note that only the somaesthetic response is inverted.

Olfactory. Blowing ammonia gas into the nostrils leads to a temperature rise in Ammon's horn. The maximum, 0.01°C., is reached in about 100 seconds and the return to the basal level lasts another 150 seconds. With the needle heated, there is an initial cooling and a later warming. No responses were obtained in non-olfactory regions. The results indicate a combination of vasodilatation and increased neural heat production.

DISCUSSION

A local control of brain blood vessels, by chemicals produced or consumed by cells in their immediate vicinity, has long been postulated (*e.g.*, Roy and Sherrington, 1890); and direct evidence of an increased blood supply to an active brain region has been accumulating (Alexander and Revecz, 1912; Cobb and Talbott, 1927; Schmidt and Pierson, 1934. See the reviews by Wolff, 1936, and Gerard, 1938, for additional literature). The present findings further substantiate this view, as do the more detailed localization experiments of Santha and Cipriani (1938), performed since these were completed. Presumably CO_2, always produced by normal brain cell activity and a powerful dilatant, is the main agent for linking the increased food and oxygen supply with the increased metabolic need for them.

An evaluation of the active brain metabolism, itself, in terms of the temperature rise on receptor stimulation, is more difficult. The total duration of the increased temperature, 6 minutes, is reasonable for the delayed heat production of brain; but the tardy and slow appearance of the rise is contrary to

expectation. Possibly the cooling effect of an increased blood flow, which sets in promptly, is responsible for the slow rise; indeed the occasional presence of an initial temperature fall requires such an interpretation. Quantitatively, as discussed, brain temperature should rise some 0.003°C. per second of continued maximal activity, providing that no heat loss occurs and that the total heat produced over several minutes is summed. One minute's stimulation would produce almost 0.2°, the temperature rising progressively until the delayed heat is all developed. Actually, of course, heat is being steadily carried away and the initial temperature rise is delayed while the maximum is reached early and not maintained. The actual rise observed, 0.015°C., is perhaps a reasonable resultant between extra heat production and continued heat loss.

Summary

A thermocouple placed by means of a Horsley-Clark instrument in determined structures of the cat's brain is used to record absolute temperatures and changes under anaesthesia or stimulation.

The brain loses heat through the cranial structures so that normally there is a temperature gradient from surface to interior, the cortex being 1.4° cooler than basal regions.

Because of this heat loss, the brain may be cooler than the blood reaching it, though normally it is warmer.

Anaesthetics (nembutal, ether) lower brain temperature (relative to that of the blood) and the temperature curve can be used to follow anaesthetic action.

Optic stimulation causes a temperature rise only in the visual system of the brain; somaesthetic stimulation a rise, less sharply localized, in the cutaneous system; and olfactory stimuli in the olfactory one.

The temperature changes are due in part to extra heat produced by the active neurons, in part to local vasodilatation induced by metabolic products of these active neurons.

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ON AN IPSILATERAL MOTOR EFFECT FROM CORTICAL STIMULATION IN THE MACAQUE MONKEY*

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DURING stimulation of the motor and premotor cortex of the rhesus monkey (*Macaca mulatta*), under light ether or Dial anesthesia, with current pulses of low frequencies (from 2 to 4 per second) and of adequate shape and duration (Wyss and Obrador, 1937; Wyss, 1937) a typical ipsilateral response has been observed in the forelimb. The region of the cortex from which to obtain these effects lies on the border between areas 4 and 6 around the superior precentral sulcus. The ipsilateral response appears as a slow tonic movement including flexion of all fingers and flexion in the elbow and shoulder joint, and represents a movement of a smooth and even character even when elicited with a rate of stimulation as low as 2 per second. No intermittent contractions synchronous with the current pulses could be observed, as is the case in an ordinary response from the contralateral motor or premotor cortex.

This ipsilateral response in the arm was always accompanied by a contralateral complex movement either in the leg or in the arm depending on whether the (bipolar) electrodes were placed above or below the superior precentral sulcus. Especially in the latter instances the contrast in the type of contraction between the two sides was most striking, both effects starting after about the same latent period. Whereas at these low frequencies the contralateral response was a clonic progressive movement (described in a preceding paper as "premotor effect"), the ipsilateral one appeared to be a pure tonic contraction. No difference in the time excitability could be found between these two types of cortical response, the optimum current duration (rising phase for double condenser discharges) being for both from 10 to 20 milliseconds.

An analogous response in the ipsilateral leg was observed only once but was much less characteristic.

Ipsilateral effects from stimulation of the cortical motor and premotor areas of the macaque have been reported by several authors (for references see Bucy and Fulton, 1933). Recently a thorough analysis of the ipsilateral representation in the motor and premotor cortex of the monkey has been made by Bucy (1933) and Bucy and Fulton (1933). On stimulating near the superior precentral sulcus they usually obtained extension in the ipsilateral lower extremity although occasionally ipsilateral flexion occurred in the upper extremity. They also demonstrated, by the persistence of these ipsilateral responses after contralateral hemisection of the spinal cord as well as after removal of areas 4 and 6 of the opposite hemisphere, that these ipsilateral

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responses are independent of the contralateral responses and that their projection system most probably occupies the ipsilateral half of the nervous system.

The ipsilateral response described in this report seems to be identical with the ipsilateral flexion in the upper extremity obtained only occasionally in the work of Bucy and Fulton (1933). With an appropriate type of stimulating current it has been possible to demonstrate that the described ipsilateral response is quite different in character from an ordinary contralateral effect. It seems unlikely that such a *tonic* mechanism should serve as basis for a bilateral representation of volitional power in one-half of the cerebral cortex.

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ON THE KINETICS OF RECOVERY DURING THE REFRACTORY PERIOD IN FROG'S NERVE*

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SINCE THE refractory period is defined in terms of absolute or relative inability of stimuli to effect a response, it is evident that in theory, at least, it may also be defined in terms of the kinetics of the excitatory process as they are described, for example, by the strength duration curve.

According to most hypotheses of excitation, the excitatory states, p, produced in resting tissue by stimuli of equal durations but of varying strengths, V, vary as V, i.e.,

$$p = V \times \text{constant}. \tag{1}$$

In the writer's most recent analysis (Blair, 1936), for example,

$$p = \frac{KV}{k}(1 - e^{-kt}) + \frac{AV}{a}(1 - e^{-at}) \tag{2}$$

for rectangular stimuli, the A's and K's, large and small, being constants. When t is constant this reduces to equation (1).

It seems likely that during the refractory period one of the variables might be the rate of accumulation of the excitatory state per unit stimulus which is given by K of equation (2) on neglecting the second term of the right. This neglect does not affect the argument but it allows the use of K instead of a more complex expression with the same meaning (Blair, 1936). Another probable variable is h the threshold of p. There is no way, however, of distinguishing the separate variations of K and h but only of their ratio K/h. It will be convenient therefore, to let S denote the state of the tissue as it is described by K/h.

It will be observed that in equation (2) if t is constant and small enough that kt is small, a condition usually satisfied in refractory period measurements, the term $(1-e^{-kt})/k$ reduces to $t=$constant so that variations in k are undetectable. There is evidence in any case (see later) that k does not vary. Also the term in A and a which are probably physical factors, is probably constant when t is constant. Thus again using K to include also the terms in A, equation (2) reduces to constant $=K\ V/h=SV=K_0V_0/h_0$, i.e., KV/h will be a constant of value given by the resting value of K_0V_0/h_0 or

$$\text{constant} = KV/h = K_0V_0/h_0. \tag{3}$$

Therefore, during the absolutely refractory period, V being infinite, $S=K/h=0$, or, in other words, the conditions existing in the tissue either will not

* Read at the Rochester meeting of the National Academy of Sciences, October 25–27, 1937.

permit the accumulation of an excitatory state at this time or the threshold h is infinite. During the relatively refractory period, K/h will increase from zero finally to attain its normal value, K_0/h_0.

The simplest kinetics to assume for the recovery of S from 0 to S_0 during the relative phase are that the rate of recovery varies as the amount of recovery still to be made, or

$$\frac{dS}{dt} = \beta(S_0 - S) \tag{4}$$

β being a constant, so that on integrating from $S=0$, at $t=0$

$$S = S_0(1 - e^{-\beta t}). \tag{5}$$

or

$$\frac{K}{h} = \frac{K_0}{h_0}(1 - e^{-\beta t}) \tag{6}$$

But according to equation (3) $Kh_0/K_0h = V_0/V$ so that

$$V_0 = V(1 - e^{-\beta t}) \text{ or } \log \frac{V}{V - V_0} = \beta t \tag{7}$$

t being measured from the beginning of the relative phase. Experimentally, however, t, is usually measured from the beginning of the absolute phase, the duration of which may be represented by t_0. Therefore, the data from the present point of view should conform to the relation,

$$\log \frac{V}{V - V_0} = \beta(t - t_0). \tag{8}$$

Before testing the applicability of this relation, it will be convenient to consider the general description of the refractory period in terms of stimuli of equal durations. In Fig. 1 is given a representation of the usual experimental results. Under different conditions, two distinct types of curves, such as the upper and the lower, are obtained, and a third type which is a modification of the upper. The upper curve, which is perhaps the physiologically normal type will be called hereafter the curve of simple recovery.

The lower type of curve occurs after the tissue has been excised for some time, and in acid media, and under the influence of certain drugs and ions, (Graham, 1934). This curve descends transitorily below the value, V_0, of the initial stimulus and then returns rather slowly to V_0. The stage in which V is less than V_0 is called the supernormal phase, but in reality it is usually subnormal with respect to the original fresh state of the tissue, V_0 being greater than it was originally.

The other type of curve differs from the upper only in that it descends more rapidly in its initial stages. It does not appear that this type has been distinguished previously. The conditions for its appearance are not estab-

lished but may be either neutrality or alkalinity of the medium. The method of detecting it will be considered later. This type and the previous one with the super-normal phase will be called hereafter the curves of complex recovery.

Simple recovery. It is evident, on inspection of Fig. 1, that only the upper curve could possibly be represented by equation (8). This case will be considered now.

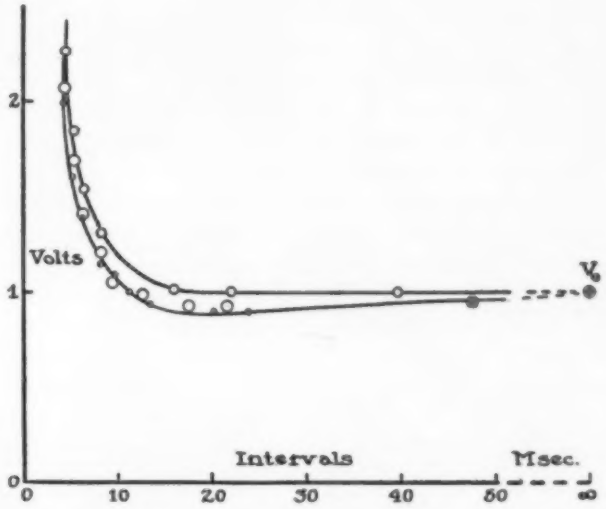

FIG. 1. The data of Table 1 by Adrian (1920, p. 18, Fig. 10) on the recovery of the frog's sciatic nerve at three different pH's. The abscissae are the intervals between the first stimuli at $t=0$ and the second, which have strengths given by the ordinates, V. The ordinate, V_0, the initial and final least adqeuate stimulus, is arbitrarily given unit value for each curve. The upper curve is for pH 8.3; the lower two, large and small circles, respectively, for pH 6.8 and 6.5 If plotted in measured volts, the curves would coincide on the left, and the lower curves would be higher on the right. The second stimuli are applied at a different point on the nerve; so the refractory phase concerned is that left by the passage of the impulse.

Equation (8) is tested easily by plotting log $V/(V-V_0)$ against t. A straight line will be obtained if the equation is valid. Fig. 2 gives a number of cases of simple recovery in the sciatic nerve of thefrog (measured by Adrian) plotted in this way. These curves are quite extensive, some going to $V=16V_0$ and the shortest going to $V=10V_0$. In this type of plotting, the divergence on the right-hand side is large for small errors, and the divergence on the left is small for large errors. Therefore it is important, in denoting the validity of the equation (8), that the points fit closely to the line on the left the short-times, end. The line cuts the time axis at $t=t_0$, the end of the absolute phase. The source of the data is given in the legend.

It will be seen that these data are linear in fair approximation. Another set, also by Adrian, is given in Fig. 3. These three curves are on the same preparation at different temperatures. The numerical data were published in this

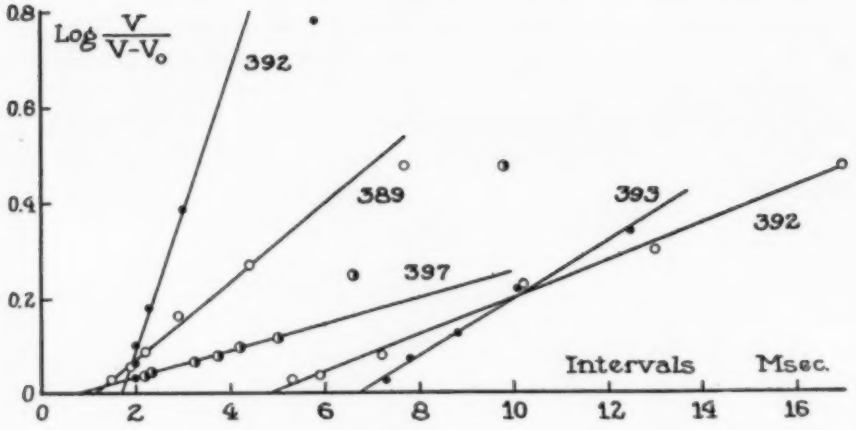

FIG. 2. Data by Adrian (1913) of simple recovery plotted according to equation (8). The lowest points in the diagram would be at about $16V_0$ if the curves were plotted as Fig. 1. The curve on the left is probably complex, of the type of those in Fig. 4. The numbers on the curves are the page numbers of Adrian's paper.

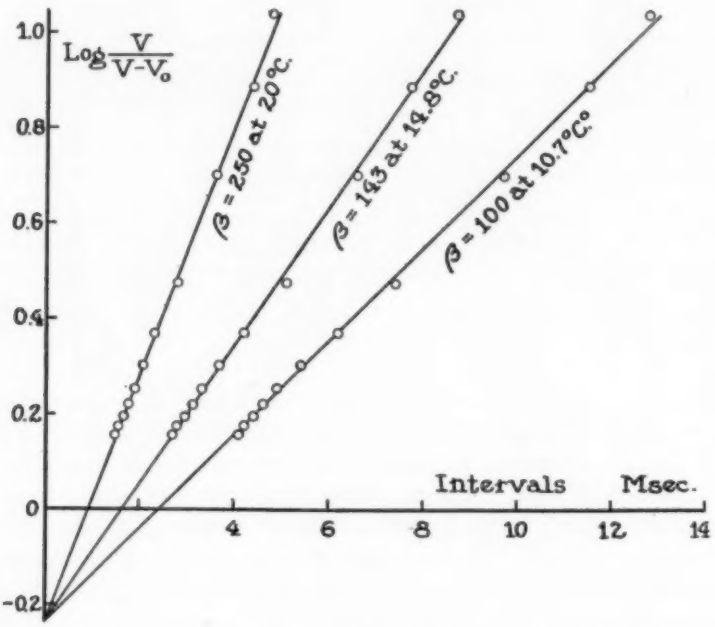

FIG. 3. Simple recovery on the same nerve at three different temperatures, as indicated; data by Adrian (1914; p. 460, exp. 1; p. 457, Fig. 1) plotted according to equation (8). The lines are extended to the ordinate axis to illustrate that the temperature changes both phases of the refractory period in the same ratio. The slopes of the lines are the constants, β, which are given below the curves. The real values, using natural logarithms, are 2.303 times as great as these.

case so they can be given more weight than those in Fig. 2 which were measured from graphs. In these cases, the conformance of the points to a linear relation is quite close throughout. Thus, the present results may be taken to indicate that the relatively refractory phase during simple recovery is defined by a state, S, of the tissue which is a measure of the ratio of the rate of accumulation, K, of the excitatory state per unit of stimulus to the amount of excitatory state, h, required to set off a response. The state, S, is zero at the beginning of the relative phase and builds up at a rate proportional to its displacement from the normal value, S_0.

Complex recovery. Of the complex recoveries, the type giving rise to the supernormal phase, as in the lower curve of Fig. 1, will be considered first. When this type is produced by acid in a tissue which gave previously the simple type, it is found (Adrian, 1920) that the curves for the two conditions tend to be coincident during the early part of recovery and that the supernormal state tends to be the same as the original normal state. That is, the supernormal phase of the lower curve (Fig. 1) would approach the upper curve without crossing it.

Therefore, in complex recovery, it may be said that the tissue sets out to recover to approximately the same point as it would in simple recovery, but that as it approaches this point some new effect enters to raise the threshold to a higher value (Adrian, 1920).

Considering now the kinetics of this type, it appears that the recovery tends initially to be given by equation (4), as before, β and S_0 being approximately the same if the same tissue is used. In the later stages, however, it seems as if the end point, S_0, must have fallen slowly to a new level. If this variable end point, P, has kinetics also like equation (4), an initial value, $S_0(1+b)$, and a final value, S_0, it may be described by $P = S_0(1+be^{-\gamma t})$, b and γ being constants and γ being small compared to β.

Replacing S_0 in (4) by P, there is obtained,

$$\frac{dS}{dt} = \beta[S_0(1 + be^{-\gamma t}) - S] \tag{10}$$

and on integrating and replacing S by V as before and measuring t from the previous stimulus instead of the end of the absolute phase, t_0,

$$\frac{V - V_0}{V} = e^{-\beta(t-t_0)}\left(1 + \frac{\beta b}{\beta - \gamma}\right) - \frac{\beta b}{\beta - \gamma} e^{-\gamma(t-t_0)}. \tag{11}$$

It can easily be seen that $V = V_0$ when $t = \infty$ and also when $t = t_1 = \frac{1}{\beta - \gamma} \log \frac{\beta - \gamma + \beta b}{\beta b}$. Also V is a minimum at the height of the supernormal phase when $t = t_2 = \frac{1}{\beta - \gamma} \log \frac{\beta - \gamma + \beta b}{\gamma b}$. From these it follows on subtraction that

$$t_2 - t_1 = \frac{1}{\beta - \gamma} \log \frac{\beta}{\gamma}. \tag{12}$$

Therefore the relation of β to γ may be obtained by measuring the interval from the time when V first reaches V_0 to the time when it reaches its minimum. If the data are frequent enough for large values of t, $e^{-\beta(t-t_0)}$ may be neglected in equation (11) and γ and $\beta b/(\beta-\gamma)$ determined from a graph like Fig. 2. Data of this kind appear to be rare, but equation (11) may be tested in another way by data by Adrian (1920).

These data are given in Fig. 1 and table 1. As may be seen in Fig. 1 there are three curves, one simple and two complex. From the simple curve, β, was obtained by means of a graph like Fig. 2. Since the other curves coincide with this initially, when all are on the same voltage scale, it is indicated that this β will apply closely to them also. Using, therefore, this β, γ was obtained from equation (12) and the other constant, b, by substitution. In table 1 are given the measured values of V and those calculated using the constants obtained in this way for all three of these curves. It will be seen that the agreement is fairly good.

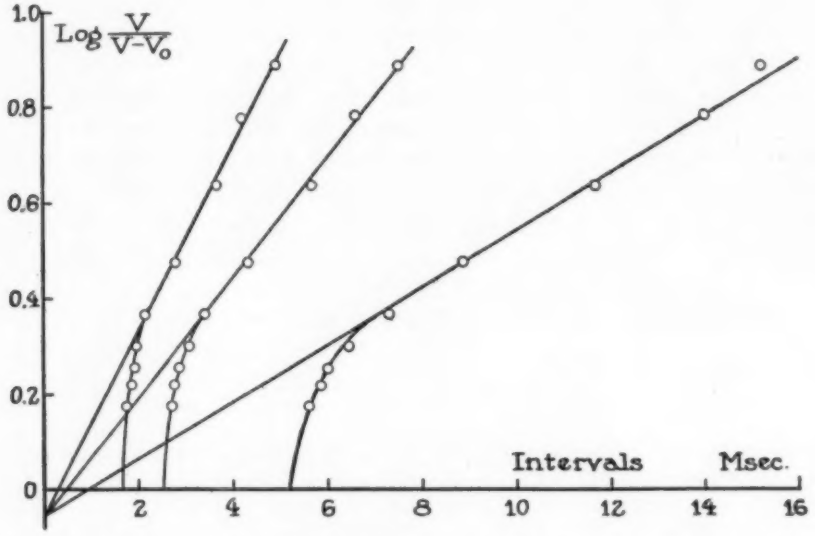

FIG. 4. Complex recovery in which γ is greater than β. The data, which are by Adrian (1914), are given in table 2. The three curves are at different temperatures. The curving downwards at the short-intervals end is due to the γ process. Adrian's Fig. 2, p. 458, gives a set of similar curves.

In the other complex form of recovery, since there is no supernormal phase, the complexity is not immediately apparent. If the data are plotted according to equation (7), however, the results are quite different from Figs. 2 or 3. In Fig. 4 are plotted a set of data by Adrian (1914) of this kind. The curves are linear for long intervals, but for short intervals the points fall rapidly. Since

the slopes of the lines are about the same as those in Fig. 3, it is immediately suggested that they again measure the constant β. But the falling away of the points at the short-intervals end suggests the addition in this phase of a much faster reaction than the β reaction. This suggests in turn that if the previous basis, equation (10), is still applicable, the constant γ has now become large rather than small compared to β. If this is the case, the term in $\gamma(t-t_0)$ in equation (11) may be neglected at long times so that this equation becomes,

$$\log \frac{V}{V - V_0} = \beta(t - t_0) + \log \frac{\gamma - \beta}{\gamma - \beta - \beta b} \tag{13}$$

which predicts lines of slope β as required for Fig. 4. Fig. 4 is plotted with t instead of $t-t_0$; therefore when $t=t_0$, the point on the time axis to which the diverging points at the short-times end are directed, the ordinate of the line is

$$\log \frac{V}{V - V_0} = \log \frac{\gamma - \beta}{\gamma - \beta - \beta b}.$$

This point, $t=t_0$ can be obtained fairly closely by inspection and more closely by trial. This is assisted in the present case by the circumstance that the set of data consists of three curves at different temperatures. For Adrian observed that on lowering the temperature, all phases of the refractory state, including the absolute period, are prolonged in the same ratio. Thus in Fig. 3, for example, the lines come together at a point on the axis, $t=0$. The lines in Fig. 4 for the long intervals meet similarly. Also there must be a point lower down on the axis, $t=0$, at which lines from each of the lowest points at the short-times end meet after cutting the axis of abscissae at $t=t_0$. Therefore, if one absolute period is determined closely, the others can be obtained by this means.

Having obtained t_0 and $\log \frac{\gamma - \beta}{\gamma - \beta - \beta b}$ as indicated, and β from the slopes of the lines, γ may be calculated from the data of short durations, using equation (11). In table 2 are given the data of these curves as observed and as calculated according to equation (11). There are some disagreements for the short intervals, notably the first point of the third curve, which is 12 per cent too high. The voltage changes very rapidly with time in this region, however, because the voltage-time curve rises very steeply, and actually this divergence corresponds to only 0.02 msec. or about 0.5 per cent in time, which is well within the experimental error. The agreement in the less sensitive regions of the curves is entirely satisfactory.

It appears, therefore, that the kinetics of complex recovery are represented adequately by equation (10), which may be pictured schematically as in Fig. 5. Here on the left is the case of simple recovery: $b=0$ so that the state, S, starting at zero at time, $t=t_0$, the end of the absolute phase, returns to its

final resting value, S_0, at a rate proportional to the distance it has yet to go. In the complex types of recovery, the one with a supernormal phase is represented in the middle. In this case, the end point, S_0, is not fixed but, starting at an initial value, P, descends exponentially rather slowly to a final level, S_0'. The time constant of this process is γ. The state, S, recovers as before at a rate proportional to the distance to the end point. But since the time constant, β, of this process is greater than γ, S transitorily exceeds S_0'. In the other type of complex recovery, γ exceeds β so that as indicated in the right-hand side of the figure, there is no supernormal phase, but the recovery of S in its later stages is too slow to be in keeping with its rate at the beginning.

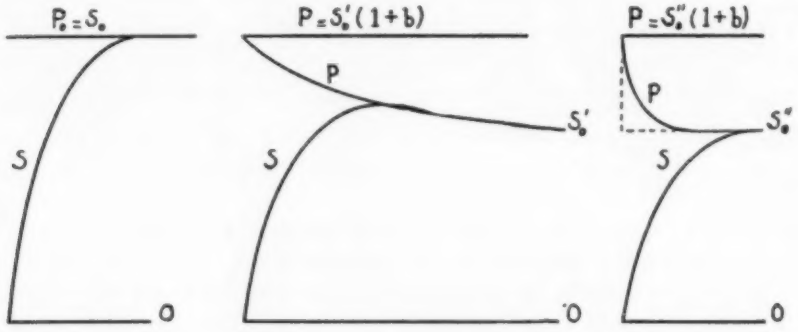

FIG. 5. Illustrating from left to right, respectively, simple recovery, complex recovery with the supernormal phase (γ small), and complex recovery with γ large. In the complex cases, the upper curves are those of the γ process, which the β process, or the state, S, approaches as end point. The reciprocals of S give the curves of the stimuli like Fig. 1. On the right, the area between the dotted coordinates and the curve of the γ process gives the recovery oxidation according to the hypothesis in the text.

It is not at all probable that, as shown in Fig. 6, the initial end points' $P = S_0(1+b)$, are the same for the same tissue under different conditions. This is approximately true, however, in the set of data of Fig. 1 and table 1, but in these cases $b < 1$. For the set in table 2, however, $b = 8$, approximately, so that $S_0(1+b) = 9S_0$. Therefore, in these cases, S_0 would be much lower than normally, or the threshold V_0 much higher if $S_0(1+b)$ were unchanged from that occurring in the tissue in the normal state.

The question arises at this point as to why the γ process does not appear in simple recovery. The obvious assumption to be made is that it does not exist, but this is neither likely nor necessary because it will be seen in equation (13) that if γ becomes increasingly large compared to β, or if b becomes small, the second term on the right will approach 0. Therefore a case of recovery in which γ is very large or b small will appear to be simple unless the data are obtained very early in the relative phase. And in fact, in several of the curves of Fig. 2, the first point tends to fall below the line, indicating that the γ process existed and was still incomplete at this stage. Therefore, it seems probable that all recovery is representable by equations (10) and (11)

and that simple recovery is but a special case of the kind outlined above. A possible reason for the smallness of b will be given later.

The factors affecting the constants. The data of Figs. 3 and 4 were taken by Adrian (1914) to determine the effect of temperature. As was remarked above, he discovered that all phases of recovery were altered by temperature in the same ratio. This is illustrated in Fig. 3 by the circumstance that all three of the lines meet at a point on the ordinate axis. The slopes of the

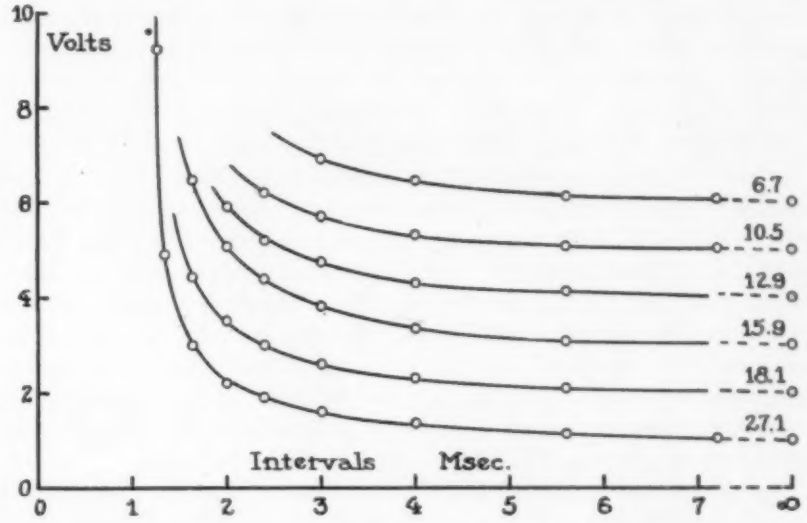

FIG. 6. The data of Blair and Erlanger (1931, p. 548, Fig. 12) on the refractory phases of different fibers in a small trunk having impulse velocities in meters per second, as indicated by the numbers on the curves. The abscissae are the intervals between the stimuli. The ordinates are volts on a scale on which the value for infinite interval is unity. The zero for each curve is the point at infinity of the curve next below. The three curves for which no point at 7.2 msec. is given were slightly supernormal in this region. This was ignored and the value of V at 7.2 msec. was taken for the value at infinity. Therefore these three curves should be slightly lower on the left side.

lines, the constants β, go in this case from 100 at 10.7°C. to 250 at 20°C., increasing about 2.7 times for a 10° rise in temperature. (The average of Adrian's results (1914, p. 463) is nearer 3.0.) β, therefore, is a function of temperature. According to Adrian's finding, and as is illustrated in table 2, γ also is the same function of the temperature with the same coefficient. The constant, b, according to table 2 is almost independent of temperature. There is no assurance from these data, however, that this process does not extend back into the absolute phase; so all that they indicate is that the value of b at the beginning of the relative phase is independent of temperature. There is other evidence, however, that the process does begin at the beginning of the relative phase (see later).

With respect to pH, β is independent according to table 1, but γ is decreased very greatly on increase of acidity, as also is b. It appears that β

tends to be independent of fiber size, according to the data of Blair and Erlanger (1933), who determined the refractory periods of several fibers in the same trunk along with the nerve impulse velocities. They concluded that both the absolute and relative phases increased considerably as the velocity decreased. On replotting their Fig. 12 (p. 548) in Fig. 6 here so that the curves for all the fibers are on the same scale, it is evident, however, that the curves for all the velocities are about the same shape and that the absolute periods are also about the same. Since β determines the shape of these curves, it appears that β does not change markedly with the velocity and therefore with the fiber size. This conclusion is probably not general, however, because in the velocity range of these data, the duration of the rising phase of the action potential changes rather little (Blair and Erlanger, 1933, Fig. 18, p. 553) with the velocity. But the absolute refractory period, at least, must increase with the low velocities for which the duration of the rising phase and therefore of the spike of the action potential is greatly increased, since it is agreed (see later) that the absolutely refractory period has about the same duration as the spike. It appears, however, that fibers with velocities in the range considered here can carry approximately the same number of impulses per second despite their differences in velocity because the recovery times are approximately equal. This property may serve some physiological purpose.

Additional relations. There are a number of additional observations concerning the refractory period which should be of use in attempting to interpret the kinetics of recovery. These will be considered now.

An important property of the supernormal phase has been determined also by Adrian (1920, p. 18, Fig. 9). This phase may be sufficiently long and stable so that during it a strength-duration curve may be taken. Adrian found that such a curve differed from that taken during complete recovery only in that it was lower throughout by a constant ratio of the ordinates. This means, in terms of equation (2), that only h or K or K/h has been altered, the constant, k, remaining as before. Therefore the assumption above of K/h as variable, k being constant, is justified experimentally for the supernormal condition. But since the supernormal condition is only a particular stage in the growth of the state, S, it is indicated that K/h is the only variable for all stages of S. In any case, the variations of k are probably small enough so that they have no effect, for the reasons given earlier.

Another observation of Adrian (1921) is that the absolutely refractory period and the duration of the spike of the action potential are approximately equal. Gasser and Grundfest (1936) agree with this conclusion.

The after-potential of the action potential which is associated with and disappears with the supernormal phase (Gasser and Erlanger, 1930) is considered by Gasser and Graham (1932) to be a manifestation of some process independent of that giving rise to the spike. This process is oxidative or gives rise to an oxidative process because the excess oxygen consumption per response on stimulation tends to vary approximately with the magnitude of the after-potential when it is greatly exaggerated by drugs (Schmidt, 1933;

Table 1

Adrian's (1920, p. 18) data for the relatively refractory phase in the same sciatic nerve of the frog at three different hydrogen ion concentrations. Temperature, 12.5°C. The times are the intervals between stimuli. V observed is calculated from equation (8) for the first set and from equation (11) for the other two.

Intervals t	V obs.	V calc.	V obs.	V calc.	V obs.	V calc.
msec.						
4.48	2.27	2.29	2.07	2.06	1.98	1.98
5.35	1.84	1.86	1.68	1.68	1.61	1.61
6.35	1.54	1.58	1.41	1.43	1.35	1.38
8.2	1.32	1.31	1.21	1.19	1.15	1.15
9.35	1.22	1.22				
9.7					1.07	1.08
9.95			1.05	1.08		
11.2					1.00	1.01
12.65			0.99	1.00		
13.5					0.94	0.96
15.9	1.02	1.04				
17.6			0.93	0.95		
20.1					0.90	0.93
21.4			0.93	0.94		
22.1	1.00	1.01				
23.8					0.90	0.93
39.8	1.00					
47.8			0.95	0.97	0.95	0.97
∞	1.008	1.00	1.00	1.00	1.00	1.00
	pH = 8.3 t_0 = 2 msec. β = 230 sec.$^{-1}$ γ = 0 sec.$^{-1}$ b = 0		pH = 6.8 t_0 = 2 msec. β = 230 sec.$^{-1}$ γ = 34 sec.$^{-1}$ b = 0.162		pH = 6.5 t_0 = 2 msec. β = 230 sec.$^{-1}$ γ = 42.5 sec.$^{-1}$ b = 0.115	

Table 2

The observed voltages and those calculated according to equation (11) (using the constants given) for complex recovery in which γ is large compared to β; data by Adrian (1914, p. 460, exp. 2). The original data were reduced to the same scale; so the observed voltages are the same for all three curves. The fluid used is described simply as Ringer's; therefore the pH is not known, but it must have been at least 7, according to Adrian (1920) since no supernormal phase appeared.

V obs.	$t-t_0$	V calc.	$t-t_0$	V calc.	$t-t_0$	V calc.
	msec.		*msec.*		*msec.*	
3.00	0.4	3.17	0.20	3.00	0.10	3.36
2.50	0.63	2.49	0.28	2.52	0.20	2.37
2.30	0.80	2.26	0.36	2.27	0.26	2.15
2.00	1.25	2.00	0.58	1.96	0.33	2.02
1.75	2.10	1.76	0.90	1.77	0.53	1.81
1.50	3.70	1.51	1.80	1.50	1.15	1.51
1.30	6.50	1.30	3.20	1.28	2.00	1.30
1.20	8.80	1.20	4.10	1.21	2.55	1.22
1.15	10.00	1.16	5.00	1.15	3.30	1.15
1.00	∞	1.00	∞	1.00	∞	1.00
	T = 9.0°C. t_0 = 5.20 msec. β = 138 sec.$^{-1}$ γ = 2600 sec.$^{-1}$ b = 7.85		T = 15.2°C. t_0 = 2.50 msec. β = 288 sec.$^{-1}$ γ = 5800 sec.$^{-1}$ b = 8.4		T = 20°C. t_0 = 1.65 msec. β = 437 sec.$^{-1}$ γ = 9500 sec.$^{-1}$ b = 9.2	

Schmidt and Gasser, 1933; Gasser, 1934, reviews this point of view). The after-potential, being associated with the supernormal phase, is therefore associated also with the process of time constant, γ. It appears probable, therefore, that this γ process is oxidative. That γ increases with alkalinity is consistent with this view since the rates of oxidative processes in tissue increase with alkalinity.

It will be observed incidentally in these regards that when γ is large, as in table 2, the negative after-potential will be so close to the spike and over so quickly that it will be distinguishable with difficulty, in accord with common experience.

Now if the process of time constant, γ, is an index of an oxidative process, the question arises whether or not it measures its rate directly. If it does, then will the area under the curve of the γ process measure the amount of recovery oxidation. The area concerned will be that, for example, between the dotted coordinates in the right-hand side of Fig. 5 and the curve above it. As can easily be seen, the area under this curve is,

$$\int_0^\infty S_0 b e^{-\gamma t} dt = \frac{S_0 b}{\gamma}. \tag{14}$$

Therefore, according to the hypothesis, bS_0/γ measures the amount of oxidative recovery. But if this is true, it is to be expected that this quantity will remain approximately constant as γ varies, for it is not likely that the energy for recovery will be very different in different cases, so long as the factors producing them are not extreme. In table 2, for the 15°C. case, $\gamma = 5800$, and $b = 8$, so that $b/\gamma = 0.0014$. In table 1, the supernormal curve at pH 6.5 and at 12.5°C., $\gamma = 42.5$, $b = 0.16$, and $b/\gamma = 0.0038$. Therefore, in spite of the great difference in γ, the quantity b/γ is of the same order of magnitude in these two nerves which are at approximately the same temperature. Presumably, S_0 is not greatly different; so the areas under the curves are about the same. It seems probable, therefore, that the γ process is a transient excess of the rate of some oxidative process above its resting value. And the extent to which it has proceeded is a measure of the state of oxidation which it has produced. This matter is discussed by Gerard (1932) and related to the heat production which he found to be of the same mathematical form as that assumed for the γ process.

With respect to the variation of b/γ with temperature in Fig. 5, $b = 8$, approximately, for all three curves, or, in other words, the oxidative rate, after a response, is increased by the same fraction of the basal rate at all temperatures, but γ is more than three times at large at 20° as at 10°. Therefore, since b/γ is one-third as great it must be assumed that only one-third as much recovery is necessary at 20° as at 10°, providing S_0 is invariable with temperature. There is no information on the dependence of S_0 on temperature in these data, but it can be shown that as the temperature is varied, keeping the duration of the stimulus constant, $h_0 = K_0 V_0$, approximately. But h_0/K_0 decreases somewhat as the temperature increases (Blair, 1935, p. 310).

Therefore S_0 increases with temperature. The increase is probably slower, however, than the decrease of b/γ. Therefore, according to the present hypothesis, the nerve will recover more economically at higher temperatures as far as the process of time constant, γ is concerned, *i.e.*, there will be less oxidative recovery per nerve impulse. This may not apply to the total energy however. For the γ process may be operated from an oxidative reserve, and the replenishing of the reserve may be more expensive under one condition than another.

The absolute period. The only direct information on the absolute period from these data is Adrian's observation that its temperature coefficient is the same as that of the relative phase. That is, when temperature alone is varied, $\beta t_0 = \text{constant}$, and also $\gamma t_0 = \text{constant}$. When the pH is varied, however, both β and t_0 remain constant but γ varies greatly. It appears, therefore, that if there is any association at all, β and t_0 are related, but γ and t_0 may be quite independent. The relation of β to t_0 suggests that these factors depend in turn on the same property of the system. Therefore, if the nature of the β process becomes known, the nature of the absolute phase may become apparent, or vice versa.

It was concluded by Adrian that in his experiments the strength of the initial shock did not modify the recovery even in the cases in which this was measured at the same place. This may not always be true, however, according to the results of a number of investigators. Erlanger and Blair (1931) and Blair and Erlanger (1933), for example, have investigated the effect of shocks of either polarity given in the absolute period on subsequent recovery. It appears that a shock from the cathode during the absolutely refractory period increases the absolute period without modifying the curve of the relative period (1933, p. 546). The effect of the anode (1931, p. 125) is not determinable unambiguously from the data given, but it may be the reverse. The observation that the cathodal shock prolongs the absolute period. and other considerations, led Erlanger and Blair (1931) to postulate that the relative phase is the disappearance of what they call the postcathodal phase of depression, following the action current spike as stimulus. This idea is used also by Rashevsky (1933) and Monnier (1934). It will be referred to later.

The nature of the processes. It is evident that a possible interpretation of the γ process is as follows: at the beginning of the relative phase, the rate of some oxidative process is found to have a value, $S_0(1+b)$, and this rate subsides exponentially to a value, S_0, which is the resting metabolic rate of the tissue. In an acid medium or in other media giving rise to a supernormal phase of recovery, b is usually small, *i.e.*, the rate of oxidation at the beginning of the relative phase is not much above the resting value, S_0; therefore recovery takes a long time and the subsidence of the oxidative rate of the resting level is slow, *i.e.*, γ is small. In an alkaline medium b is large, *i.e.*, the oxidative rate at the beginning of the relative phase is much above the resting rate. Recovery, therefore, takes place rapidly, and the resting rate, S_0, is soon attained, *i.e.*, γ is large. The total excess oxidation is perhaps usually

about the same in both acid and alkaline media. But there are cases, simple recovery, in which it appears, as was mentioned above, that γ is unusually large or b is unusually small so that b/γ, the oxidative recovery, is small. This may be a property of fresh preparations in which recovery may be very economical, or it may be that recovery is accomplished by a different method. And there are other cases of the opposite kind in which, under the action of drugs, the supernormal phase is very prolonged, *i.e.*, γ is extremely small and b is probably large so that b/γ the oxidative recovery, is unusually large (Schmidt and Gasser, 1933).

Since the γ process has an electrical sign, it is implied in the above conclusion that the resting metabolic rate, S_0, or the factors which determine this rate, may determine also the resting membrane potential. Therefore, since the negative after-potential accompanying the γ process is a lowering of the membrane potential, it is indicated either that an increase in the rate of oxidation involves a decrease in the membrane potential, or that a lowering of the membrane potential brings about an increase in the rate of oxidation. The latter alternative is the more probable, however, because the membrane potential is low on asphyxiation and recovers with oxygen (Furusawa, 1929; Gerard, 1930, 1932, p. 510) indicating that the state of oxidation determines, or is related to, the membrane potential. Also, in asphysia (Amberson, Parpart and Sanders, 1931) the after-potential becomes less and less evident. This may be because it disappears very slowly, if at all, since the oxidative process required to reduce it is absent, and the membrane potential becomes progressively lower. Therefore it appears likely that the membrane potential during the γ process is low because the state of oxidation is low, and because the state of oxidation is low the rate of oxidation is excessive until the state of oxidation is brought back to normal.

The β process is independent of the γ except that its end point is determined from moment to moment by the stage which the γ process has reached. In accord, therefore, with the assumption above that the γ process is oxidative, the rate of oxidation, or the factors which determine this rate, determine also the extent to which the β process will proceed. It scarcely can be considered that this process has any part in restoring the membrane potential since it apparently has no electrical manifestation, and particularly since it does not start until after the action potential spike has subsided, *i.e.*, until the membrane potential has returned to, or nearly to, its normal value. It appears, therefore, that this β process involves only the restoration of the ability of the tissue to respond to stimuli. Thus the excitability is a property which is added, to, or is recovered by, the system after it has regained in large part, at least, the organization which determines its potential.

At present, there does not seem to be any conclusive evidence either from the data of excitation or of recovery to indicate the nature of the quantity K/h and therefore of this β process. It cannot be defined any further, therefore, than as a return of excitability in this particular sense.

It may be suggested, however, that the excitability-substance of Osterhout

and Hill, (1933) is involved. For if this occurs in nerve and is lost by the irritable structure during the response the β process may be the reacquisition of this substance by the membrane or its recombination with the elements of the membrane.

The relation of β and γ to the time constants of excitation. It is inconsistent with present considerations to assume that the constant, k, of equation (2) the excitability in the usual sense, is related to β. Furthermore, k changes markedly with the velocity of the impulse (Erlanger and Blair, 1933; Blair, 1934) in the range in which β does not, according to Blair and Erlanger (Fig. 6 above). The numerical value of k is greater also, being several thousands instead of hundreds for the frog's sciatic nerve. It is similarly unlikely that k is related to γ since k is much less dependent upon pH. There seems to be a possibility, however, that β and γ are related to the time constant of inhibition (Rashevsky, 1933), or accommodation (Monnier, 1934; Hill, 1935). The reason for assuming this possibility is as follows: if the oxidative process during recovery is associated with an alteration of the membrane, potential, it is very probable that an inadequate electrical stimulus, or any stimulus before it becomes adequate, which will change the membrane potential, will also in consequence disturb the resting oxidative equilibrium and initiate a γ process. This, in turn, should bring about a β process leading to a new state, S_0, corresponding to a new value of K/h. Therefore, during stimulation it may be necessary to take into account these factors which may be the same as inhibition. Since this matter can be investigated experimentally, however, it will serve no useful purpose to speculate upon the nature of the relations until the appropriate data are available. The observation of Blair and Erlanger (1931) that the postcathodal depression and the relative refractory phase disappear in about the same times is very suggestive that β determines both, but it is obvious that the dependence of γ on pH will allow a rather large variation in the experimental results; so from this point of view their results are special cases. There is another difficulty, too, that the postcathodal depression does not always occur in frog's nerve and muscle (Blair, 1936); whereas the refractory phase and presumably, therefore, the β process always does.

The negative and positive after-potential. It will be evident that recent work on the after-potentials particularly of mammalian nerves (Gasser and Grundfest, 1936) (Lehmann, 1937) requires a more complex representation than has been given. For in these nerves the composite of after-potential phenomena is oscillatory, consisting of a negative potential followed by a positive then by a negative and so on, resembling a damped mechanical oscillation of increasing period. The excitability is super- and sub-normal in step with the negative and positive variations. It is evident, therefore, that the representation of the γ process as a simple exponential while adequate except under special conditions in the frog will be inadequate with mammalian nerve. In this case the γ process must be represented by some appropriate oscillatory function, or as suggested by Gasser and Grundfest (1936), by two contrary processes.

These cases are so complex mathematically in relation to the accuracy of measurement that it seems likely that they can be studied most safely as extensions of the simpler situation in the frog.

Summary and Conclusions

It appears likely that by means of stimuli of short, equal durations and variable strengths one is enabled to describe the refractory period in terms of, and only in terms of, the ratios, $S = K/h$, K being the rate of accumulation of the excitatory state per unit stimulus and h being the threshold value of the excitatory state. At the end of the absolute phase, this state, S, beginning at 0 returns to its end point, S_0, at a rate proportional to the distance remaining. The end point, however, depends upon the rate of some oxidative process which is raised by the response, and which recovers exponentially to its resting value. When its recovery is fast there is no supernormal phase of excitability, but when it is slow there is a supernormal phase as well as an evident after-potential which is associated in some way with the excess oxidation. The time constant of the recovery of the state, S, has no electrical manifestation, is independent of pH, and of fiber size to some extent, is increased about three-fold with 10°C. rise in temperature, and varies inversely as the absolute period as this varies with temperature. The time constant of the oxidative process varies similarly with temperature but is increased very greatly on going from acidic to alkaline media. If both of these processes are chemical, a method is provided for studying the reactions concerned with much greater accuracy than is ordinarily possible. In any case, the mode of variation of the time constants of these processes with different reagents and conditions should throw considerable light on the nature of the excitatory mechanism and of the refractory state.

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FUNCTIONAL RECOVERY IN OCULAR MUSCLES OF A CHIMPANZEE AFTER SECTION OF OCULOMOTOR NERVE*

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I. INTRODUCTION

THE MORPHOLOGICAL changes which take place during degeneration and regeneration of peripheral nerves have been thoroughly investigated (Ranson, 1912; Ramón y Cajal, 1928; Speidel, 1935). In the case of the cranial nerves, however, information is less complete and little attention has been given to the functional aspects of the problem, especially with regard to the return of motor power following transection. Highly favorable for such a study are the muscles of the eye. The movements of the two eyeballs are synchronous and coördinate, and any differences in their coördinated actions, or in the movements of the eyelids, are therefore conspicuous. The present note is based upon study of a chimpanzee following section of the third cranial nerve. The characteristics of the oculomotor paralysis were analyzed in detail as well as the stages of regeneration and recovery of function.

II. OBSERVATIONS

Details of these observations are included in the following protocol:

Experiment 1. Section of right IIId cranial nerve in chimpanzee; complete ophthalmoplegia; "fright" reaction after 5 weeks; gradual recovery with disappearance of ptosis after 3 months and return of conjugate movements. Stimulation of left eye fields causing elevation of right lid and movement of eyeball; section of regenerated nerve abolished cortical response. Ablation of eye field. (Tim)

The subject of the experiment was a male chimpanzee in which a small flocculonodular lesion of the cerebellum had been made 6 months previously (Dow, 1938).

First operation.—On February 5, 1937 with the animal under deep sodium amytal anesthesia the right oculomotor nerve was exposed by elevating the right temporal lobe and cleanly severed with a pair of sharp scissors. The two cut ends lay separated from one another by 2 to 3 mm. after the transection. The cortical eye fields were in no way damaged by the operation.

Postoperative notes—1st day.—When the animal recovered from anesthesia, the right eye showed complete ptosis, the globe was externally deviated, the pupil maximally dilated (7 mm.), and "fixed" to all types of light stimulation; the only slight orbital movement detectable was in the horizontal plane between the outer canthus and (partially) the midline (IVth and VIth nerves). Both eyelids moved downward in response to corneal and visual stimulation and during spontaneous blinking.

5th day.—The animal had now quite recovered from the operation. Movements of the right eyeball between the outer canthus and central visual axis were more evident. Ptosis continued to be complete.

11th day.—The ptosis began to disappear; the right palpebral fissure being open 1.5 mm.; and by the 29th day (March 6) it was 4 mm. wide. Recovery developed more rapidly on the temporal than on the nasal side of the eyelid.

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31st day.—The animal had been tested several times previously for the "fright" reaction with indefinite response. Today when threatened the right fissure within about 30 seconds widened to 9 mm., remained open for 45 seconds and then narrrowed down to 4 mm. This raising of the upper eyelid associated with fright, and termed the "fright" reaction (Bender, 1938), was thus demonstrated and it proved entirely similar to the corresponding phenomenon observable in ophthalmoplegia in monkeys.

54th day.—Ptosis was still diminishing, the palpebral fissure being open 8 to 9 mm. as indicated in Fig. 1. Note that the left eyeball is looking upward.

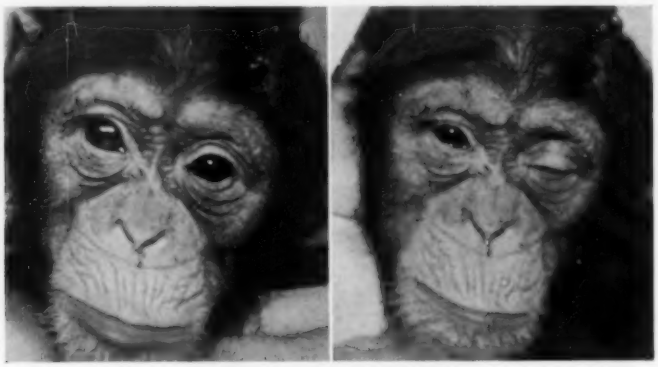
FIG. 1. Photograph taken on 54th day after section of right oculomotor nerve. Note partial recovery from ptosis of right eye (open 8 to 9 mm.) The left eye is looking upward indicating that the right must be maximally opened.

60th day—Pseudo-Graefe phenomenon.—During the period in which the ptosis had been diminishing it had been noted that the right upper eyelid did not move in unison with the normal left eyelid; thus, when the chimpanzee looked down, the left lid moved downward, whereas the right superior lid remained stationary. This phenomenon was especially noticeable today (April 6), when the affected palpebral fissure was open 10 mm. By the 81st day (April 27) it was noted that when the left eye looked down* the right upper eyelid definitely became slightly elevated (pseudo-Graefe phenomenon, Fig. 2). The latter movement was evidently due to active contraction in the recovered levator palpebrarum muscle.

Subsequent course.—After the 81st day recovery of function proceeded continuously; ptosis was less marked, the pupil became smaller (6 mm.) in diameter, and the eyeball made movements toward, but not beyond, the vertical plane of the central visual axis. This is well illustrated in photographs taken on the 102nd day (Fig. 2, A and B). On the *110th day* (May 26) it was noted that when the eyes were conjugately deviated to the left, the right eyeball moved to the left beyond the central visual axis, thus demonstrating the presence of contraction in the right internal rectus muscle. The right pupil measured 5 mm. in diameter. On gazing to the left or downward, the right upper eyelid was found to retract; *i.e.*, impulses to the right internal or right inferior rectus were accompanied by impulses to the levator palpebrarum. *In other words, several muscles innervated by the formerly cut oculomotor nerve contracted simultaneously, and the levator palpebrarum contracted when it should have relaxed.* In order to ascertain whether these contractions

* When the chimpanzee looked down only the left eyeball rotated toward the lower lid edge. Vertical movements in the right globe were not apparent, probably because the depressor and elevators of the eye contracted simultaneously. Proof that this was the case was found in a monkey in which the inferior rectus muscle was divided and the oculomotor nerve cut. When regeneration appeared, upward and inward movements of the eyeball and simultaneous retraction of the lid occurred.

en masse were related to the oculomotor nerve regeneration, stimulation of the eye center in the cerebral cortex was carried out. Horizontal movements of the globes, if thus induced (in which the right internal rectus muscle would take an active part), should be accompanied by a retraction of the right upper eyelid. The assumption was that the cortical stimulus directed to the internal rectus would be conducted along the regenerated oculomotor nerve to the levator and other ocular muscles.



A B

FIG. 2. Photographs of eyes on 102nd day after right IIId nerve section. A. Complete recovery from ptosis in right eye. The right eyeball, however, is still deviated outward. B. The pseudo-Graefe phenomenon: the *left* eyelid descends in looking down but the right upper eyelid remains contracted and right globe moves slightly toward the midline.

A B

FIG. 3. Return of ptosis after resection of the regenerated right oculomotor nerve. A. Looking upward. B. Looking straight ahead.

Second operation—Stimulation of cortical eye fields (Area 8).—On May 26, 1937, under ether anesthesia, the right and left cerebral hemispheres were both exposed and various points, particularly those of the eye fields, stimulated (see Fig. 3) with faradic current, and also by the Wyss and Obrador (1937) double condenser stimulator. Observations on the effects of stimulation were made before and after section of the reunited oculomotor nerve. Bipolar and unipolar electrodes were both used.

Third operation—Resection of the right IIId nerve.—After the eye fields had been stimulated the right oculomotor nerve was again reexposed and found firmly reunited; it was again severed with scissors. Thereafter the animal again developed complete ptosis of its right eye (Fig. 3; see below).

Fourth operation—Ablation of left eye fields.—Some hours after the previous operation the left frontal eye fields (area 8) were ablated by Dr. Margaret Kennard who will describe the results in another connection.

SUMMARY OF FINDINGS

1. Stimulation of the fields in the *right* cerebral cortex resulted in conjugate deviation of eyes to the opposite side.* The globe moved slightly past the midline toward the left while the right upper eyelid retracted.

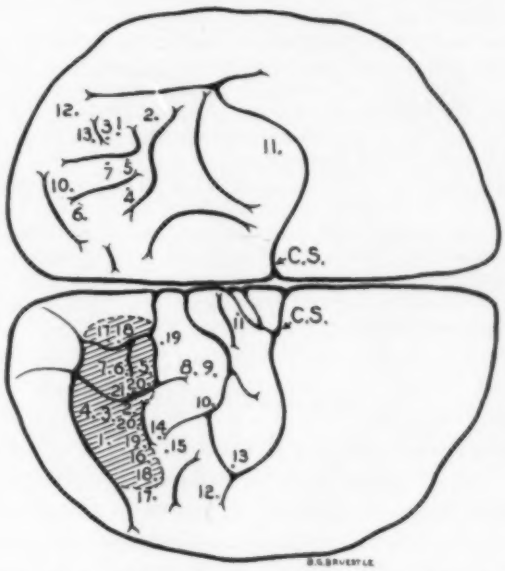


FIG. 4. Diagram of the hemispheres showing the principal points stimulated in outlining the eye fields. For key to points see *Appendix*.

2. Stimulation of eye field in the left cerebral hemisphere yielded conjugate movement of eyes to the right (Fig. 4). The right upper eyelid became slightly elevated with these ocular movements.

3. Section of the reunited oculomotor nerve 110 days after it was first cut resulted in the reappearance of ophthalmoplegia (Fig. 3) and external strabismus; there was at first no dilatation of the pupil, since the pupil had for another purpose been constricted by instillation of eserine 5 hours prior to the resection of the IIId nerve. After the effects of eserine had worn off the dilatation of the pupil became evident.

4. Stimulation of the eye fields following the second cutting of the right oculomotor nerve failed to elicit movement in the right superior eyelid or right internal rectus muscle. When the right cortical eye field was stimulated to cause the eyes to move conjugately to the left, the right globe moved, but only to the midline (Fig. 4). This movement was interpreted as due to relaxation of the right external rectus muscle (Sherrington, 1893, 1899).

* Repeated stimulation causing the eyes to move to the left was followed by conjugate deviation of eyes to the right when at rest. This was interpreted as relaxation in the fatigued group of muscles and thus secondary deviation of the eyes by the non-fatigued group of muscles.

Postoperative notes (*Fourth operation*).—When the chimpanzee recovered from the anesthetic one hour after resection of its IIId nerve, in addition to the right oculomotor ophthalmoplegia, the left eye was found deviated to the left. Rarely did the left eye move beyond the midline to the right. This restriction of eye movement to the right seemed to be part of supranuclear conjugate paralysis as a result of extirpation of the left eye field (Kennard and Ectors, 1938). The head was turned persistently to the left and when the animal walked, it invariably turned to the left, the eyes moving first, then the head, then the neck and upper trunk, the rotation movements occurring in spiral fashion. The fields of vision were normal; the animal reacted to confrontation tests in the right as well as the left fields of vision.

Four hours after the operation, the head and eye deviation toward the left became less prominent, although the animal still tended to rotate toward the left in its movements. Six hours after operation the head was practically in the midline, the left eye was slightly deviated to the left and the animal when attempting to move, did so to the left. When the left eye moved to the left, the right eyeball moved from the outer canthus to the left, but only to the midline. Eighteen hours after operation the general condition was the same. When in motion, the chimpanzee circled toward the left.

After 24 hours the right and left cerebral cortices were reexposed and the eye fields were again stimulated. No responses were obtained on stimulating the right eye field at this time. Subsequent stimulation, however, caused the left eye to move out to the left, while the right eye moved toward the midline.

Fifth operation—Ablation of right occipital lobe.—The right occipital lobe was then ablated on May 27, 1937. Following this procedure, both eyes were found conjugately deviated to the right. So long as the chimpanzee was under deep anesthesia, the eyes remained deviated to the right. When the anesthesia was light, the eyes returned to the midline position. Stimulation of the cerebellar hemispheres produced no responses either in the eyes or in any of the extremities. The animal was then sacrificed (May 27) under deep anesthesia for histological study.

III. Discussion

The muscles supplied by the oculomotor nerve are the superior, inferior, and internal recti, levator palpebrarum, inferior oblique, pupillary constrictor sphincter and ciliary muscles. When this nerve is electrically stimulated, all structures innervated react. The resultant visible effects are retraction of the superior eyelid by the levator palpebrarum muscle, internal rotation of the globe by the internal rectus muscle, and constriction of the pupil by the sphincter constrictor fibers.* Vertical movements of the globe are not apparent because the action of the inferior rectus is antagonistic to that of the superior rectus and inferior oblique muscles. When these contract simultaneously there is little resultant motion. Furthermore, the action of the internal rectus is enhanced by the fact that the antagonistic muscle, the external rectus, is relaxed. With such apparently reenforced action, the eyeball is pulled on a horizontal plane nasally rather than in any other direction. On electrical stimulation of the normal oculomotor nerve, discrete action in individual muscles could not be obtained.

After section and regeneration of the oculomotor nerve in the chimpanzee, a similar picture was obtained. It appeared that all muscles, never one, contracted. Whenever the inferior or internal rectus muscle was stimulated to contract, there occurred retraction of the superior eyelid and inward move-

* These observations were made in monkeys in which the normal and regenerated oculomotor nerves weve electrically stimulated (M.B.B.).

ment of the globe. Vertical rotation of the eyeball was not observed. Identical conditions have been described in the human (Bender, 1936). Pupillary constriction as noted on electric stimulation of the normal oculomotor nerve was conspicuously absent. Apparently regeneration to the pupillary sphincter muscle had not take place. However, some evidence for recovery in this structure may be found in the gradual lessening of the pupillary dilatation; that is, return of tone in pupillary constrictor muscle. Active contraction of the pupil in association with an impulse to the inferior rectus muscle in a man who showed evidence of oculomotor nerve regeneration has been described (Bender and Alpert, 1937). The constriction of the pupil in this case was part of a contraction of all structures innervated by the oculomotor nerve.

With regard to this apparent lack of pupillary function in the chimpanzee, it must be remembered that when the oculomotor nerve is cut intracranially, the fibers degenerate only as far as the ciliary ganglion. When regeneration occurs, the fibers reunite with cells in the ciliary ganglion and not the m. sphincter pupillae directly. The nerve endings in the ciliary muscle did not degenerate. These factors may play a rôle in the delayed recovery of function of the pupillary constrictor fibers. Perhaps with time, pupillary movements might have been detected.

The phenomenon of simultaneous contraction in muscles supplied by a regenerated nerve with loss of individual action has an anatomical basis. In numerous experimental studies, morphological evidence of nerve regeneration has been found as early as one day after the nerve had been cut. Axons from the central stump grow out into the exudate and break up into many branches, making, as is well known, a compressed regenerating mass of fiber. The axons in the peripheral stump do not occupy the nerve sheaths corresponding to those of the central stump. Furthermore, intermingled with the axis cylinders of the medullated nerve fibers are those of the non-medullated type.

With such structural alterations a stimulus conducted in the central stump along a set of fibers which normally supplies one group of muscles is shunted at the scar by way of the regenerated axis cylinders to fibers which carry impulses to other groups of muscles. Thus contraction of individual muscles would be impossible. The degree of contraction in each of the recovered muscles would depend on the number and variety of regenerated nerve fibers it received. Some muscles, like the levator palpebrarum in the chimpanzee described, might be reinnervated chiefly by fibers of the inferior rectus and internal rectus, and but little by branches from other nerves in the central stump. Such regeneration would explain why the upper lid retracted on downward and nasal gaze but not on upward gaze.

Summary

1. Observations of functional recovery following section of the oculomotor nerve of a chimpanzee are recorded.

2. Inward or attempted downward movement of the affected eye caused

the formerly ptosed eyelid to retract. Attempted downward gaze was also accompanied by an inward movement of the globe.

3. These phenomena were effected through a reunited oculomotor nerve, and not by other nerves, since identical responses were obtained with electrical stimulation of the cerebral cortex. After the reunited nerve had been severed, all responses were abolished and the ophthalmoplegia reappeared.

4. The elevation and retraction of the upper eyelid was part of contraction en masse of muscles supplied by the regenerated oculomotor nerve.

5. The contractions en masse are explained by undifferentiated and disorderly regeneration of the axis cylinders in the distal stump.

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APPENDIX: STIMULATION EXPERIMENTS

Stimulation of left cortex with unipolar electrode Harvard inductorium. (*Begun at 11 a.m.*) (Fig. 4).

1. The eyes deviated to the right and then to the right and upward. Later the left eye turned to the left and upward while right eye turned to the right and then to midline. (Right oculomotor nerve cut on Feb. 5, 1937.) The right pupil had eserine at 10. a.m.
2. No response.
3. Both eyeballs to the right.
4. Both eyeballs to the right; twitching of the lids.
5. Both eyeballs to the right; while the lids were closed.
6. Both eyeballs to the right; both lids opened but the left opened before the right.
7. Both eyeballs to the right.

8, 9, and 10 were premotor movements of the right upper extremity.

11. Right foot movement.
1. Repeated, eyes to the right, a 6 second latency.
12. Right lip (mouth drawn to the right).
13. Right thumb movement (adduction and flexion).
14. No response.
15. No response.
16. The lids opened, the right upper eyelid before the left.

1. Repeated. Eyes moved promptly to the right and the lids opened. (Induction coil at 9.5 cm.)
3. Repeated. Eyes deviated to the right.
16. Repeated. Eyes deviated to the right and lids opened—latency 8 seconds.
17. No response.
18. Eyes to the right and then the lids opened.
19. Eyes to the right and then the right eyelid pulled up.
20. Both eyelids opened. There was no movement of eyeball.
4. Repeated. Eyes moved to the right.
21. No response.

Stimulation of right cortex—11:50 a.m. Chart II.

1. Left eye to extreme left; right eye to left slightly beyond the midline. Both upper eyelids raised but the right much more than the left.
2. Same as under 1.

12:20 p.m.

1. No response.
3. Left eyeball to left; right to midline. Right eyelid opened.
1. Right eyelid open 6 mm. Right eyeball to the midline. Left eyeball to left.
4. Left eyeball to left.
5. Left globe to left, right globe slightly to the left. Right eyelids opened slightly.
6. No response.
7. No response. Animal in deep ether anesthesia. The left pupil has been getting gradually larger until now it is 5 mm. in diameter.
2. Repeated. No response.
3. Repeated. Left eyeball to the left. Right eye slightly to midline.
5. Repeated. No response.
2. Repeated. Left eyeball slightly to left.
2. Repeated. Eyelids opened right more than left.
3. Repeated. No response.
12. Repeated. No response.
13. Repeated. No response.

} Cortex inactive. Both eyeballs deviated most of the time to the right.

1:30 p.m. Stimulation of the left cortex. (Fig. 4).

4. Repeated. Eyes turned promptly to the right.
3. Repeated. Eyes turned promptly to the right.
1. Repeated. Eyes turned promptly to the right.
5. Repeated. No response.
3. Repeated. Both eyes to the right; eyelids slightly open.
17. Repeated. No response.
18. Repeated. No response.
19. Repeated. No response.
20. Repeated. Head turning and inclining to the left.

ELECTRICAL EXCITABILITY OF THE MOTOR FACE AREA: A COMPARATIVE STUDY IN PRIMATES*

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I. INTRODUCTION

ANALYSIS of functional localization in the cerebral cortex has led to a progressively closer correlation with structural characteristics. The important pioneer studies of the Vogts[15] were the first on the cytoarchitecture of functionally discrete cortical areas. Investigations of the effects of ablation of the arm and leg areas in monkeys and anthropoids have recently been carried out by Fulton and his collaborators[7] but the areas controlling movements of the face, head and neck have been little studied and there remain many points of uncertainty. In the present study the effects of localized cortical ablation of the face area have been observed as well as the characteristics of its excitability. In order to correlate electrical responsiveness with structural detail, histological examination by serial section has been made of the experimental brains. The results will be presented in two papers, the first dealing with the excitability and the second with the effects of ablation of the "face area" of the cerebral cortex and its component parts.

Historical review

The responses of the facial musculature to cortical excitation were studied in detail by Beevor and Horsley.[1,2] From the inferior part of the precentral convolution they obtained a great variety of facial and lingual movements, which they described minutely. Movements of the face were most frequently observed when the upper portion of this cortex was stimulated, and lingual movements result from stimulation in the extreme inferior portion of the precentral convolution. Laryngeal movements were described about the same time by Semon and Horsley.[12] In the latter part of the 19th century Spencer[14] initiated the study of respiratory changes. Although the subject was discussed by others[9] the next important advance was made by Cécile and Oskar Vogt[15] in 1919, who described in detail the reactions to cortical stimulation of the motor face area and correlated them with the cytoarchitectural structure of the cortex. They found that excitation of the gigantopyramidal cell area (area 4) gave rise to discrete responses of the cephalic musculature with a low threshold of stimulation. From the area just rostral to this, area 6a$_\alpha$, with somewhat stronger stimuli, more complicated movements arose. Just inferior to this area, about the sulcus subcentralis anterior, was a zone (area 6b$_\alpha$) from which rhythmical masticatory movements of the tongue, jaw and pharyngeal muscles were obtained. Stimulation slightly anteriorly (area 6b$_\beta$) produced alterations in respiratory rate and rhythm. In the intact cortex rhythmical movements of the tongue and jaw were seen with stronger stimulation of area 3a (lower part). The experimental findings of the Vogts have been confirmed in man by Foerster[6] and Cushing,[5] but histological correlations could not be made with clinical studies. The respiratory changes evoked by cortical stimulation have

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been studied recently by Smith,[13] and by Bucy and Case.[4] These authors report inhibition of respiration by stimulating a small area in the oral part of the human precentral gyrus.

Methods and technique

Animals. The responses to electrical cortical excitation have been studied in 33 monkeys (*Macaca mulatta*) of which 3 were in such poor condition that no results were possible, 4 baboons (*Papio papio*), 4 chimpanzees (*Pan satyrus*), 1 mangabey (*Cercocebus aethiops*), and 1 spider monkey (*Ateles ater*). The cortex in the face region was intact in 29 animals; 11 had one or more cerebral ablations of the motor or premotor face area at least one month previously. The latter animals make it possible to demonstrate the effect of excitation of the various cytoarchitectural areas in the absence of adjacent regions. In some animals superficial cortical incisions were made at the time of stimulation, but this, as commonly occurs, often led to dubious results because of "shock" and depression of cortical activity.

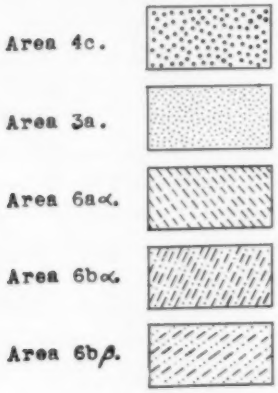
Stimuli. The cortex was excited by several methods. In the early experiments (17 occasions) the Harvard inductorium was used. Later (12 cases) stimulation was obtained by repeated condensor discharges through a thyratron tube and loosely coupled step up transformer, while still later a sixty-cycle A.C. sine wave (13 cases) current was employed. Galvanic stimulation was used in 3 experiments, the source being one or two 6-volt storage batteries in series. In many experiments the several forms of stimulation were compared. Bipolar metal electrodes, separated 2 mm., were used. As a routine procedure the cortex was stimulated for 5 seconds with 1 minute between tests.

Respiratory tracings. Respiration was recorded on smoked paper, by attaching a recording tambour to one arm of a tracheal cannula or to a partially inflated blood pressure cuff fastened around the thorax.

Histological control. At the time of stimulation representative points were marked on the cerebral cortex with india ink. The brain was later fixed in formalin or 95 per cent alcohol and the cortical markings of the inferior frontal region indicated by ink lines traced upon cellophane. The inferior frontal region with a generous amount of adjacent cortex on all borders was embedded in celloidin and sectioned serially at 20 to 25 micra, every 25th section being stained with toluidin blue or thionin and mounted. These sections were studied microscopically, and every 50th drawn at a magnification of 2, the cytoarchitectural areas being marked upon the drawing. Every operated cortex and a number of normal ones were so treated. In all, the brains of 22 animals, including chimpanzees, baboons and macaques, have been studied in this manner, representing more than 40 hemispheres; in 2 baboons and 2 macaques the cortex of the face area was sectioned serially and stained for myelin according to the Weigert-Pal technique.

Terminology. The terminology used in the description of the cortical areas follows that of the Vogts in their description of the cortex of *cercopithecus.* The term motor cortex or motor area will be used as synonymous with area 4 and premotor interchangeably with area 6 (Fig. 1).

The following abbreviations and symbols have been used:



C. S. . . . . sulcus centralis
I. P. . . . . sulcus precentralis inferior
S. A. . . . . sulcus subcentralis anterior
S. S. . . . . sulcus Sylvii

II. The Morphology, Anatomical Relations and Architectonics of the Face Motor Area

The configuration of the inferior portion of the precentral convolution of the macaque and baboon is usually constant. Near its inferior extremity, the central sulcus swings posteriorly to terminate half a centimeter above the sylvian fissure. Between the central sulcus and the vertical limb of the inferior precentral sulcus (frequently termed the arcuate sulcus) lies a triangular area bounded inferiorly by the sylvian fissure. In its middle is a small dimple, a rudimentary sulcus, termed the *sulcus subcentralis anterior* (Fig. 1). A fairly constant feature of the macaque and baboon cortex is a small vein passing from the horizontal limb of the precentral sulcus inferiorly and posteriorly to the central sulcus joining the latter approximately a centimeter from its lower extremity. This vein is an important landmark, for excitation of a point in the superior angle between it and the central sulcus almost always gives rise to flexion of the contralateral thumb, and stimulation of a point in its inferior angle produces retraction of the contralateral angle of the mouth. The face area then consists of a triangular area between the inferior limb of the precentral sulcus anteriorly, the above mentioned vein and the central sulcus posteriorly, and the sylvian fissure inferiorly.

Anatomical relationships. The afferent connections of the cortex of the face area are of two types, one subcortical and the other cortical. The main subcortical projection arises from the medial portion of the anterior half of the lateral nuclear mass of the thalamus.[16] This projection terminates almost entirely in area 4, only a few fibers passing to area 6. The significance of this connection lies in the fact that the afferent connections of this part of the

thalamus are from the dentate nucleus of the cerebellum. It is probably through this mechanism that the cerebellum maintains a coordinating influence upon the volitional motor activity of the cerebral cortex. Transcortical connections are numerous from both the postcentral convolution and the prefrontal areas (Mettler[10,11]). The efferent projections from this area are not so well known. Mettler[10] and Levin[8] have both studied Marchi degenerations from lesions of this area in the monkey. We have also examined three preparations serially sectioned after being treated according to Marchi technique. The lesions were confined respectively to the motor and premotor areas, the premotor area, and the motor area. In general, a projection system passes

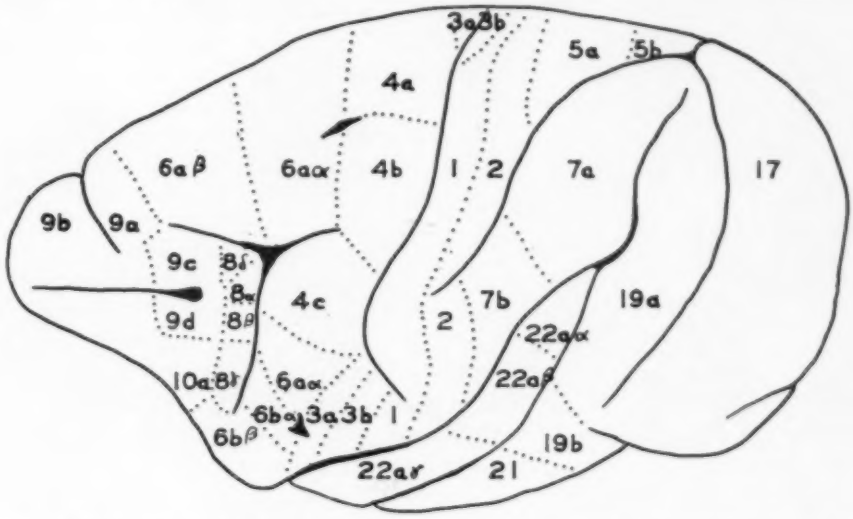


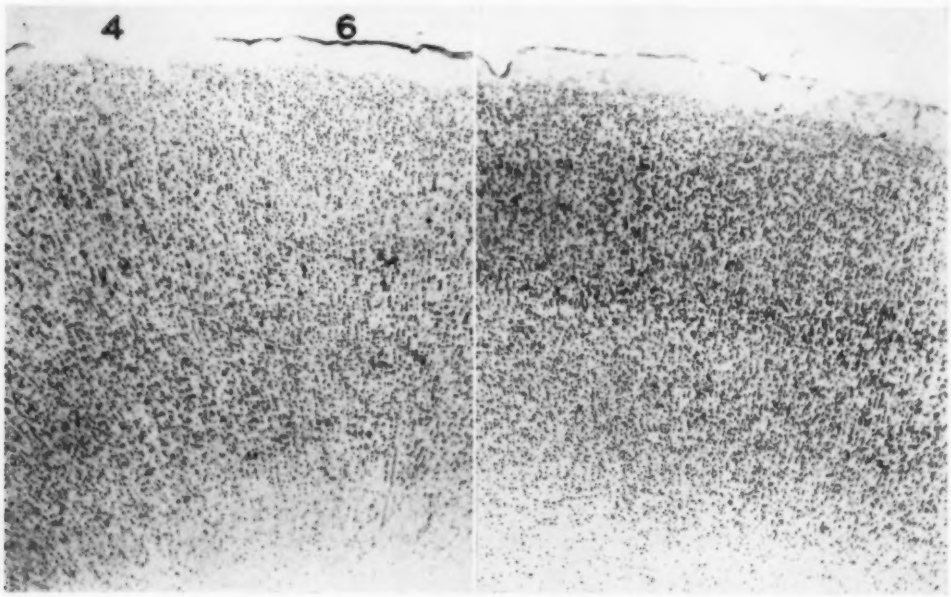
FIG. 1. Cytoarchitectural divisions of the cerebral cortex of the cercopitheque monkey according to the Vogts' investigation.

from both the motor and premotor areas, through the knee of the internal capsule and the medial third of the peduncle to the pons. In its course fibers are given to the thalamus, substantia nigra and subthalamic regions. In the pons numerous corticopontine fibers break up in the dorsal pontine nuclei. Corticobulbar fibers leave the main group of descending fibers in the cerebral peduncle to lie at the ventral border of the tegmentum adjacent to the medial lemniscus. From there fibers pass into the tegmentum and reticular substance, but no bundles reach any of the cranial nerve nuclei. Presumably an intercalated neuron is present or these fibers arborize about the dendrites of the cells of the cranial nerve nuclei.

Cytoarchitectural pattern. Within this area are several distinct cytoarchitectural and myeloarchitectural divisions. Although the general architectural characteristics of this part of the precentral convolution conform to those of the superior portion, it has certain unique features. The motor (area 4) and premotor (area 6) regions are readily distinguished and the latter may be sub-

divided into three distinct parts. In the posteroinferior corner of the face motor area the sensory cortex (area 3) extends anterior to the central sulcus.

Area 4. This portion of the face region presents the general characteristics of the gigantopyramidal area, *i.e.*, thick, agranular cortex with comparatively large, sharply staining Betz cells in the fifth layer. These cells do not reach the enormous size of those in the leg and arm areas, rarely attaining a diameter of 50 micra nor are they found in the same profusion as in the latter areas. They are not uniformly dispersed, but occur more frequently along the upper part of the central sulcus and are sparsely scattered anteriorly (see Fig. 2A). Superiorly the area extends from the central almost to the inferior precentral sulcus but tapers inferiorly to the anterior lip of the central sulcus.



A B

FIG. 2. Photomicrographs to show the cytoarchitectural appearance of the cerebral cortex of the face motor area. A. Areas 4c and 6aα. B. Area 6bα.

Area 6. Lying anterior to the gigantopyramidal area and extending to the depth of the inferior precentral sulcus is a zone of agranular cortex, area 6aα, presenting the same characteristics as that bordering the gigantopyramidal area in the arm and leg areas. It is, in fact, in direct continuity and indistinguishable from that portion (see Fig. 2A). Immediately inferior to this area, with a fairly abrupt transition, is a distinct type of agranular frontal cortex characterized by a heaping up of the medium sized pyramidal cells just below the fourth layer, giving the appearance of a dense granular fourth layer (see Fig. 2B.) This area 6bα is quite characteristic and readily distinguished. It extends as a strip along the inferior margins of areas 4c and 6aα from the anterior subcentral sulcus to the lower portion of the inferior precentral sulcus. Anterior and inferior to this area, the cortex of area 6bα is slightly modified, the heaping of the fourth layer becoming less prominent, and the cells of the fifth layer slightly smaller. This portion is area 6bβ of the Vogts. It has a faint but definite granular layer, which traced anteriorly becomes more pronounced as this type of cortex merges into area 10.

The posterior margins of these latter two types of area 6 cortex along the anterior subcentral sulcus sharply give way to the cortex of area 3a. This sensory or granular cortex extends anteriorly from the tip of the central sulcus to the anterior subcentral sulcus

and inferiorly almost to the sylvian fissure. It is characterized by its thinness, and the presence of occasional large cells in the 3rd and 5th layers, which distinguishes it from the cortex of area 3b and 1.

Myeloarchitectural pattern. The myeloarchitecture of the divisions of the face area is not quite so distinctive as the cytoarchitecture. In myelin stained preparations area 3 is characterized by its thinness, and the presence of a dense transverse layer of myelin fibers in the fourth layer. In the motor or gigantopyramidal area, the increased thickness of the cortex is more apparent and the transverse bands less prominent. In area 6 the latter is still less pronounced.

III. The Results of Electrical Stimulation of the Face Area

Electrical excitation of each cytoarchitectural area causes a more or less characteristic response which may be modified by an interplay between the constituent parts of the motor areas. It is therefore necessary to consider the response of the individual parts of the face area to electrical stimulation both in the intact normal cortex and in the isolated cytoarchitectural area, for the latter response while not physiological is essential for an analysis of the part played by each cortical area in a movement.

The principal areas

Area 4. The characteristic response from electrical excitation of area 4 of the face region is a brief contraction of an individual muscle of the contralateral face or a smooth sustained contraction of a group of muscles (see Fig. 3). The fine twitch of a small group of muscle fibers is best elicited by galvanic excitation of the motor cortex; sustained responses may be obtained by faradic or sinusoidal stimulation. The threshold of excitation of the cortex within the area is not uniform; usually from a small area along the anterior lip of the central sulcus in the upper part of the face area, a minimal stimulus, insufficient to elicit a response from any other part of the face area, will give rise to retraction of the contralateral angle of the mouth. With the same stimulus, this response may be carried to any part of the motor face area by facilitation, *i.e.*, successive stimulation of adjacent points. It cannot be carried with this minimal stimulus into the suprajacent arm area or into area 6, although a somewhat stronger strength of excitation will allow this response to be carried to area 6 of the face region. Slightly stronger stimuli will give rise to other primary responses from area 4, in general the response is in the facial musculature when the upper part of the cortical face area is stimulated, and in the tongue when area 4 near the tip of the central sulcus is excited. The usual response of the tongue is deviation and rotation to either side, but many variations may be present. Movements of the soft palate may result from stimulation of this lower part, but vocal cord movements have not been observed. With slightly supraliminal stimuli, parts of area 4 may give a response while intermediate points are unresponsive. This phenomenon is probably related to the scattered collections of Betz cells, especially since such cells are most numerous in the superior portion of area 4 (face part) lying along the anterior margin of the central sulcus, from which area a response is produced by minimal stimuli.

These characteristic responses from area 4 are present even after area 6 has been removed. In fact, if all but a few Betz cells are ablated, a typical response may still be obtained from these remaining cells. It therefore follows that the response from area 4 is independent of any adjacent cortical areas. However, a certain interrelationship of areas 4 and 6 may be shown with slightly stronger stimuli. If the point with minimal threshold in area 4 is

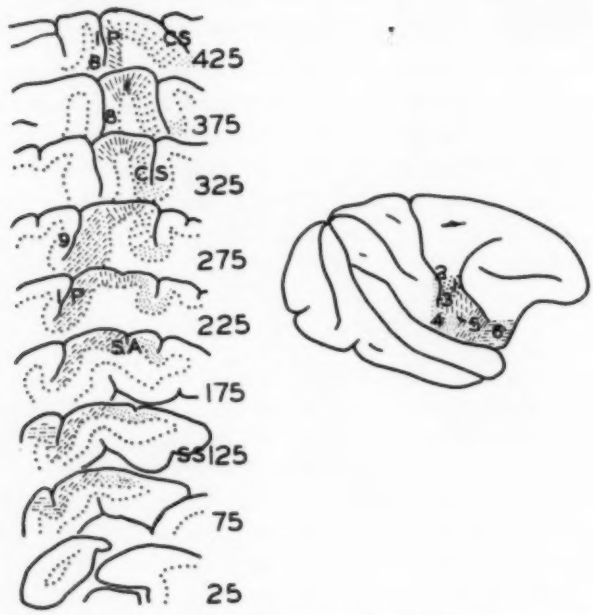


FIG. 3. (Area 6, 59) Sketch of the right cerebral hemisphere to show the cytoarchitectural areas of the face motor region in a macaque monkey, and representative sections of the same cortex to show the precise limits of the different areas. The following responses were elicited by electrical excitation with a sine wave 60-cycle alternating current:

Point 1. (2 volts) Retraction of the left angle of the mouth.
Point 2. (2 volts) Elevation of the left shoulder.
Point 3. (2 volts) Protrusion and slight deviation of the tongue to the left side.
Point 4. (2 volts) No response.
Point 5. (2 volts) Rhythmical opening and closing of the jaw with backward and forward movement of the tongue.
Point 6. (5 volts) Arrest of respiration (see Fig. 6).

stimulated with a liminal stimulus, the response may be obtained from adjacent parts of area 4 by facilitation, but cannot be carried to any adjacent areas. With slightly stronger stimuli it is possible to facilitate the response into area 6a and carry it to the boundaries of this area. With somewhat stronger excitation the response may be carried into areas 6b, 3 and 1 (Fig. 5). It cannot be carried into the arm region, for as soon as the boundary between the face and arm region is passed the face response is lost and a finger movement appears.

Area 6. In general the threshold of area 6 is definitely higher than that of area 4. Responses from area 6, contrary to those from area 4, cannot be carried by facilitation, because stimulation of an adjacent cortical point gives rise to a new response.

Area 6a$_\alpha$. Each of the three cytoarchitectural subdivisions of area 6 have more or less specific responses to electrical excitation. Excitation of area

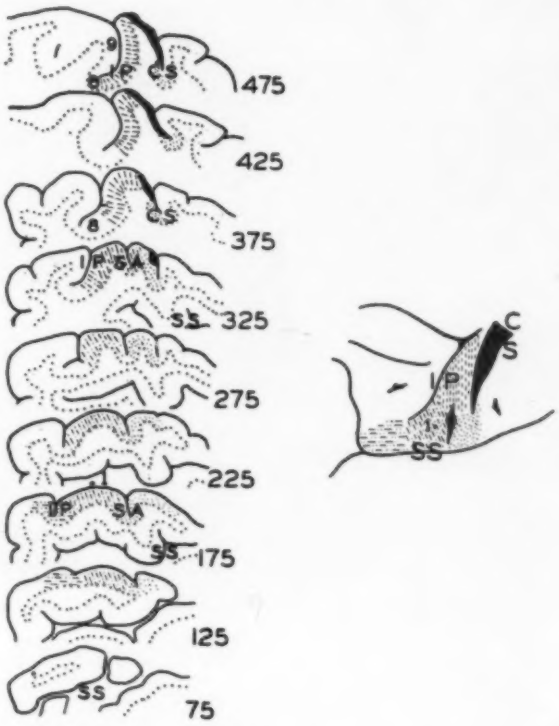
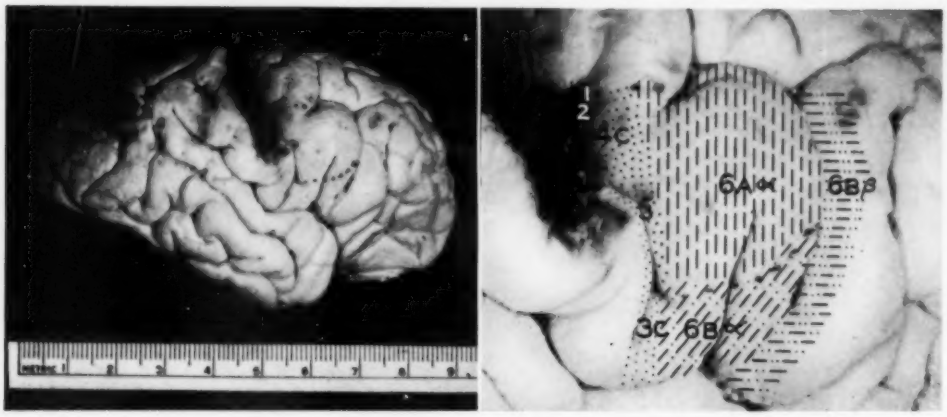


FIG. 4. (Area 6, 68) The cytoarchitectural areas of the motor face area of the baboon (*Papio papio*). In this animal area 4 was completely removed 5 months previously (the ablated area is in black). Excitation of the entire remaining face region caused no motor response except from the area surrounding point 1, from which rhythmical chewing movements of the jaws and tongue were elicited. The point was marked with india ink, and its precise position as revealed by serial sections of the cortex is shown in section 175.

6a$_\alpha$ gives rise to rather complex movements of groups of facial muscles, but never to twitches of individual ones. Entire ablation of area 4 largely destroys the responsiveness of area 6a$_\alpha$ (Fig. 4). Strong stimuli cause, after a latent period, feeble rhythmical masticatory movements from its lower part if 6b$_\alpha$ is intact, but a superficial incision between areas 4 and 6 (made in area 6, 1–2 mm. from the border of area 4, in 5 experiments) does no more than temporarily impair the response. After 15–20 minutes the shock passes off and the cortex responds as formerly to the same strength of stimulus. It is there-

fore probable that the responses seen from area 6aα are the result of short subcortical U fibers between it and area 4.

Area 6bα. Excitation of area 6bα with stimuli slightly suprathreshold for area 4 produces a characteristic response consisting of rhythmical opening and closing of the mouth, with or without protrusion and retraction of the tongue. This response may be maintained for a long period of time, but cannot be carried by facilitation to adjoining parts of the cerebral cortex. It is quite independent of the adjacent cortex of area 4, and persists in the



A B

FIG. 5. (Chimp. S.) A. normal size. B. Enlargement of the cortical face area to show the cytoarchitectural areas. Using 10½ volt galvanic stimuli the following responses were obtained:

Point 3. Twitching in the contralateral side of the tip of the tongue.

Point 2. Twitching in the contralateral cheek muscles.

No responses could be obtained outside area 4 with this form of excitation. Stimulation of point 3 with 1½ volt sine wave 60-cycle current produced deviation of the tongue to the left side. This response could be produced from any point in area 4 by facilitation but as a primary response from point 3 only. Using a stimulus of 2.5 volts it could be facilitated to any point in areas 4c and 6aα but not to area 6bα or 6bβ (within the area outlines in A). Primary responses elicited by a stimulus of 2.5 volts were as follows:

Point 1. Extension of the left thumb.

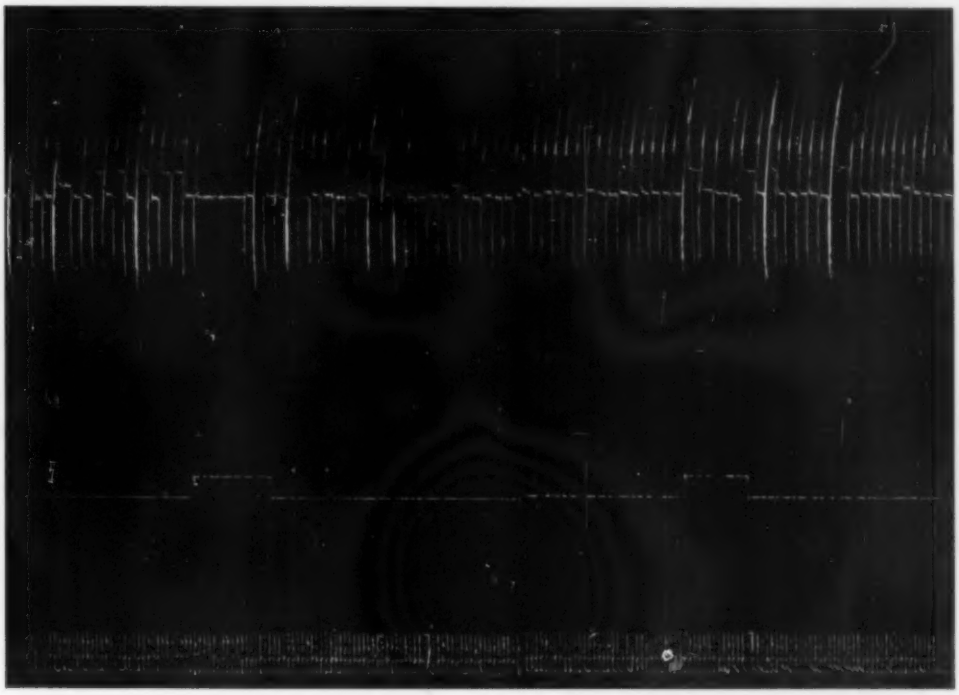
Point 2. Retraction and elevation of the left upper lip.

Point 3. Deviation and protrusion of the tongue to the left side.

complete absence of area 4. Rhythmical movements of jaw, tongue and pharynx are readily elicited in the monkey and baboon but in the chimpanzee we were able to produce only rhythmical movements of the tongue. Beevor and Horsley[1] were also unable to elicit masticatory movements in the orang. In the intact cortex these rhythmical movements may be associated with slow complex movements of the tongue before the onset of the rhythmical component (see Figs. 3 and 4).

Area 6bβ. Excitation of area 6bβ in five of 15 experiments, 10 monkeys, 2 baboons and 3 chimpanzees, in which respiration was recorded produced an

alteration of the respiratory rate and depth (Fig. 3). Respiration is usually completely arrested in expiration for 10–15 seconds, although after 9–10 seconds a respiratory effort may break through (Fig. 6), and occasionally only a diminution of excursion is present. Although respiration was arrested



A B

FIG. 6. (Area 6, 59) Respiratory record showing, A. complete temporary arrest of respiration following stimulation of area 6bβ (point 1, Fig. 3). B. slowing of the respiratory rate from stimulation slightly anterior to point 1 of the previous tracing at the junction of areas 6bβ and 6bα. (The strength of excitation was 5 volts using a 60-cycle sine wave stimulus; respiratory record is a tachygram recorded from the tracheal cannula; time is shown in seconds at the base of the record.)

in expiration in all our experiments other investigators have described its cessation in forced inspiration or expiration and in normal inspiration or expiration.[13,4] The response is quite independent of the motor area or other portions of the premotor cortex. The best results were obtained from the monkey, but were observed in the baboon and chimpanzee.

Area 3a. Area 3 which extends anterior to the central sulcus is inexcitable in the absence of area 4. In the intact cortex, however, strong stimuli produce simple movements of the facial musculature or of the tongue. Similar movements have been observed from excitation of the postcentral convolution (area 2). Incision of the cortex superficially does not abolish these responses

but deep incision does. It seems probable, therefore, that such responses are the result of subcortical connections to area 4, although spread of current is not excluded.

Ipsilateral cortical representation

It is difficult to produce isolated movements of the mm. orbicularis oculi or frontalis from cortical stimulation, but in 2 experiments we have seen them; usually the response is bilateral, occasionally only contralateral. In only one instance have we seen ipsilateral contraction of the lower facial musculature as the result of cortical excitation. In one experiment excitation of area 8 elicited a protraction of the contralateral pinna.

The tongue, however, has extensive bilateral representation in the cerebral cortex. Section of one hypoglossal nerve (6 experiments) causes only a moderate poverty of lingual movements. When the cerebral cortex contralateral to the section is stimulated, practically every movement of the tongue, deviation to both sides, rotation, protrusion, and rhythmical movements, may be elicited. The range of movement especially to the contralateral side is impaired and the denervated half of the tongue is only passively moved, but the response from ipsilateral cortical stimulation is still so rich that casual observers have suggested that the nerve section was incomplete. Subsequent section, however, of the second hypoglossal completely abolishes all lingual response from cortical stimulation. The ipsilateral responses may be just as readily obtained from area 4c as from areas 6aα and 6bα.

Other effects from cortical stimulation

Other responses to excitation of the cortical face motor area were carefully observed. We have never seen pupillary alteration or eye movements although these often result from stimulation just anterior to the inferior precentral sulcus in area 8.

Inhibition. On numerous occasions we have attempted unsuccessfully to inhibit the artificially induced response by excitation of the opposite cerebral cortex. The usual effect of such simultaneous bilateral stimulation is to complicate the movement with a second component. This is particularly evident with comparable points producing lingual movements. In one experiment we have been able repeatedly to inhibit the rhythmical tongue movements elicited from area 6aα by stimulating the ipsilateral prefrontal granular cortex just anterior to the vertical limb of the inferior precentral sulcus (area 9c). We have also been able to inhibit the shivering under ether anesthesia by stimulation of areas 6bα and 6bβ.

In one case in which the lateral three-fourths of the cerebral peduncle was sectioned (histologically verified) no effects were obtained from stimulation of the face area. Excitation of area 8 produced good eye movements, and excitation of the upper part of area 6aα gave good ipsilateral responses in both the upper and lower extremities but none in the contralateral ones. Inhibition of voluntary movements and of ether postures also followed stimulation of the anterior part of this area.

Vocal cord movements. Vocalization as the result of cortical excitation was elicited in only one experiment. Movements of the vocal cords, however, frequently followed excitation of area 6bα in the macaque. These may occur in the absence of respiratory change and are bilateral.

Salivation. Frequently in the course of an experiment profuse salivation has been noted. Quantitative measurement proved impracticable and we can only say that excitation of the face motor area produces a definite augmentation of salivation, area 6 being somewhat more efficacious than area 4.

Epilepsy. Many investigators have noted that after prolonged excitation of the motor cortex, epileptic afterdischarge is frequent. We have had the privilege of stimulating several animals, previously used by Dr. R. U. Light in his studies on induced epilepsy. The tendency for an epileptic discharge to occur in these animals was so great that discrete responses could only be obtained by the use of liminal stimuli for 1–2 seconds; longer excitation even with these weak strengths produced an epileptic discharge.

IV. Discussion

The present investigation largely confirms the original studies of Cécile and Oskar Vogt.[15] The division of the electrically excitable cortex, giving rise to cephalic movements, into areas having characteristic responses allows some insight into the function of the cerebral cortex. The proximity of the cortical areas concerned in the control of respiration, salivation and lingual, pharyngeal and laryngeal movements is evidence of nature's economy. Through simultaneous integration of these autonomic and somatic processes, which are physiologically intimately related, the cortex maintains a harmonious and well coordinated masticatory and deglutitory mechanism. Were not the respiratory movements so regulated, the danger of aspirating food would indeed make swallowing a hazardous process for the individual.

Such an analytic study indicates some of the possible roles which each part of the motor cortex may take in the normal performance of the brain. The functional divisions of the cortex are so interrelated that the activity of one modifies that of the other. This interplay is a fundamental process which has developed through phylogeny with the progressive differentiation of the cerebral cortex.

In rodents electrical stimulation of the cerebral cortex gives rise to rhythmical movements of the jaw and tongue but isolated single movements of the face or tongue are rarely seen. In these animals there is little cytoarchitectural differentiation between the component parts of the excitable cortex. In the carnivora, although cortical development has proceeded, individual muscle responses are still rare. It is not until the motor and premotor cortex become distinct, as in the lower primates, that discrete movements are readily elicited. With further differentiation, such as that present in the higher anthropoids and man, the generalized primitive response recedes and the discrete becomes more prominent. With this process of encephalization and cortical differentiation, a mechanism develops, as Foerster[6] and Fulton[7] have

emphasized, for the control and coordination of the activity of the differentiated motor responses. Subserving this function for the cephalic muscles is area 6aα (lower part). As has been shown, this area appears to operate through its adjacent cytoarchitectural zones, in the absence of which it is unresponsive. It is this portion of the face motor area which shows the greatest development in phylogeny (compare Figs. 3, 4 and 5) reaching its acme in man.

Summary

1. The cytoarchitectural characteristics of the face motor area of the macaque monkey, baboon and chimpanzee are discussed, and their response to electrical stimulation described.

2. From area 4, the characteristic response is a brief contraction of an individual muscle or group of muscles.

3. Stimulation of area 6aα gives rise to rather complex movements of groups of muscles; removal of the adjacent areas abolishes the response.

4. Rhythmical masticatory and deglutitory movements are obtained from stimulation of area 6bα; these responses are independent of the adjacent cytoarchitectural areas.

5. Stimulation of area 6bβ causes changes in the respiratory rhythm.

6. There is extensive bilateral representation of the tongue in the cerebral cortex.

7. Vocal cord movements and sialorrhoea have been obtained from stimulation of area 6.

8. The phylogenetic and physiological significance of these cortical responses is discussed.

It is a pleasure to acknowledge the generous suggestions and stimulating criticisms and encouragement given us by Professor John F. Fulton. We want also to thank Dr. D. Denny-Brown for his helpful advice during this research.

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Addendum: Since this paper was submitted for publication Penfield and Boldrey have published the results of electrical stimulation of the cerebral cortex in a large number of human subjects. Their studies do not, however, include any histological examinations of the stimulated areas. (Reference: Penfield, W. and Boldrey, E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, 1937, *60:* 389–443).

FACILITATION OF REFLEX ACTION IN THE SPINAL CAT FOLLOWING ASPHYXIA OF THE CORD FROM CYANIDE AND INCREASED INTRA-SPINAL PRESSURE

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THE EFFECT of asphyxia on the spinal cord is sometimes lost sight of because of its more striking effects in relation to respiration. That asphyxia is a powerful stimulant to the spinal cord is well known to all who have worked with the spinal animal which exhibits violent convulsions as soon as artificial respiration is discontinued. The violence of this stimulation and its sudden onset have tended to distract attention from the fact that in asphyxia, as in strychnine poisoning, there is a stage, preceding the convulsions, of simple facilitation or spread of reflex action, no movement occurring unless a sense organ or nerve is stimulated. The injurious effect of asphyxia on reflex arc conduction rather than this early beneficial effect, has been emphasized, following Sherrington's (1906) original statement of the greater dependence of the reflex than of a nerve trunk on oxygen. But loss of reflex irritability occurs only during the later stages of extreme asphyxia, while more moderate asphyxia must be a much more frequent condition among animals as they meet the emergencies of life.

Moderate asphyxia of the spinal cord improves conduction and results in a spread of reflex activity. Sherrington (1909) in his early work on the spinal cat, found the scratch reflex more easily elicited under slight asphyxia. Graham-Brown (1909) confirmed this on the spinal guinea pig, and more recently Gesell and his co-workers (Gesell and Moyer, 1935; Winkler, 1929, 1930; Glazer, 1929, and Gay, 1930) have reported that in various types of asphyxia the reflex contraction of the dog's tibialis anticus was higher than with an adequate oxygen supply. These results were not uniform however and in many instances asphyxia acted deleteriously on the reflex instead of beneficially. The whole dog was used, under morphine-urethane anaesthesia and the irregular results are doubtless in part due to the effect of the anaesthetic. We think it likely that this anaesthesia, pushed to the surgical point, affected the spinal reflex threshold, for unpublished results show the delicate reflex preparation here used to be sensitive to much smaller morphine injections than required to act on the whole animal.

Our evidence favors the view that only synaptic junctions or reflex centers are involved when the reflex improves in slight asphyxia. (Gesell *et al.*, believed nerve and muscle were also affected.) Observations were made on the spinal cat without anaesthesia and using a minute muscle as a delicate

* With the assistance of H. J. Frachtman in some experiments.

indicator of conduction in the reflex arc. Diminution of the oxygen supply to the cord, either by injection of cyanide or by increased intraspinal pressure, invariably caused a greater contraction due to an increase in the number of motor units involved, *i.e.*, to a facilitation or improved synaptic conduction. Further, this degree of tissue asphyxia had no detectable effect on the motor nerve or the muscle and by inference none on the sensory nerve, so the improvement was entirely due to spread of conduction within the "motoneurone pool" of the particular muscle concerned. Finally, the increased discharge of motor neurones is not due to asphyxial stimulation of them, but only to a facilitation of conduction, since no contraction occurs except as a result of sensory stimulation.

Method

The cat is etherized, carotids tied and brain destroyed, much as one would pith a frog (See Porter and Allamon, 1936). The cord also is pithed down to the lower thoracic region. The right hind leg is denervated and the tenuissimus muscle of the left leg is prepared for registration.* This muscle is so small in the cat that both as a nerve muscle and as a reflex preparation it can be made to show the contraction of individual motor units.† This has been described in a previous paper by Porter and Hart (1923) using optical recording. It has since been found possible to record the contraction of individual motor units more conveniently with a long straw on a smoked drum.

The muscle is exposed as previously described (Porter and Hart, 1923). A Harvard heart lever is cut to project 2 to 3 cm. on each side of the fulcrum and a light straw, 50 cm. long, is cemented on one arm for registration.‡ The other is bent at right angles to project into the wound and is fastened to the end of the muscle as it lies immersed in Ringer's solution. The movement of the muscle is magnified about 15 times. The weight of the straw is the only tension on the muscle.

With such a straw the friction of the pointer on the drum tends to prevent a proper return to the base line after a contraction. This difficulty is largely overcome by attaching a buzzer to the stand to which the lever clamp is fastened. The slight tremor of the straw reduces friction at the writing point and it returns properly to its original base line.§

The stimuli are break shocks from a large inductorium with the secondary at a considerable distance from the primary. The primary current is

* In a series of 81 cats used for various purposes in the last three years tenuissimus has been absent in 2 cats, too small to use by our methods in 4 cats, and present and usable in all the others. Tenuissimus is also present in the dog.

† Small tail muscles also show very distinct step-like all-or-none increments and decrements of contraction both as nerve-muscle and as tonus contractions (Porter 1929), but, of course, are not suitable for a problem such as the one described in this paper, since they do not respond to electrical stimulation of sensory nerves, but only to such stimulation as causes change in tonus.

‡ These have been obtained from wholesale florists as part of wheat sheaves used for Thanksgiving decorations.

§ This device is not original with us, but we do not know who first used it. The buzzer we use is a discarded dry shaving razor which plugs into the regular 110-volt circuit. A house door-bell type buzzer works equally well.

reduced to approximately 0.1 of an ampere and kept steady with resistance wire; and a uniform shock is obtained with a copper-mercury key.

The shocks are applied to the posterior tibial nerve through a special liquid electrode which maintains uniformity (Porter and Allamon, 1936). The wound for exposing the tenuissimus muscle is arranged as a shallow cup, and the muscle immersed in Ringer's solution. It is sometimes necessary to dust the wound edges with the difficultly soluble local anaesthetic, Anesthesin (Ethyl Aminobenzoate)* to eliminate reflex tremors.

FIG. 1. Reflex contractions of tenuissimus muscle near the threshold. Contractions made up at first mainly of four motor units. (Some isolated contractions of a fifth.)

Successive intravenous injections of 1.5 per cent pheno-barbital (luminal) threw one motor unit after another out of action in all-or-none steps with complete extinction of the reflex after the third dose. Sensory stimuli (break shocks to posterior tibial nerve) unchanged during the record. Stimulation 45 per minute. Record natural size. Contraction magnified on drum about 25 times.

Since the tenuissimus originates from one of the vertebrae, it is impossible to prevent the movements of artificial respiration from causing slight undulations in the base line. To obviate an apparent variation in the height of the superposed contraction, the primary key is attached to the artificial respiration machine in such a way that a break shock is always given at the same point in the respiratory cycle. Reflex contractions, when recorded near the threshold, are seen to be of a few definite heights with no gradations between. As the stimuli are increased in strength the muscle contractions increase by definite steps (very clearly with optical recording, Porter and Hart, 1923). In Fig. 1 the initial height of reflex contraction, produced mostly by four motor units, was reduced in four steps by intravenous injections of luminal as indicated. Such steps in contraction height are almost certainly caused by single motor units, or neuro-muscular squads (Porter, 1929), passing into and out of action, and the record is thus an indication of the condition of the motoneurone pool. This is isotonic registration of the same phenomenon demonstrated by Liddell and Sherrington (1923) in their well

* In perhaps one in 15 animals we have found it impossible to control these tremors.

known isometric studies of reflex contractions of larger muscles. It is not surprising that the activity of individual motor units should be detectable by our methods, since approximately 150 tenuissimus muscle fibers are innervated by one motor axon (Adrian, 1925) and there are probably only about 50 motor units in the entire muscle (Porter and Hart, 1923). Preliminary experiments indicate that the tibialis anticus shows the coarser features of the phenomena we shall describe, but the advantages of using the finer indicator—tenuissimus—are evident.

Asphyxia of the cord has been produced in two ways: (1) by the injection of sodium cyanide, and (2) by increased intraspinal pressure, following Cushing's technique for producing increased intracranial pressure (Cushing, 1901). These methods can easily be controlled and the latter has also the advantage of sharply localizing the asphyxia to the cord.

Results

Experiments with cyanide

Cyanide acts by interfering with oxidizing enzymes so that the effect is that of oxygen want (Sollmann, 1936). Sensory stimulation was reduced until a few motor units, preferably only 2 or 3, contracted reflexly. 0.1 per cent sodium cyanide was rapidly injected into the external jugular vein, usually about 0.2 cc. corresponding to 0.1 mgm. per kgm. for the average cat. After a variable latent period (minimum 12 seconds), the height of contraction increases, often at first by only one or two steps, later by many. An example is shown in record A of Fig. 2. If a larger dose of cyanide is given, the condition passes into true convulsions which cannot be distinguished from those following strychnine injection. Cyanide is relatively rapidly altered in the body to the harmless thiocyanate (Sollmann, 1936) and within a short time after an injection, the contractions return to their original height. (Record B of Fig. 2.) We have usually allowed 10 or 15 minutes between injections, but a second can be effective 3 minutes after the first and possibly earlier.

We have made 41 injections on 13 cats. In no animal has cyanide failed to cause improvement in reflex contraction. A few separate injections have failed, but this has been attributed to the dose being too small or the injection too slow to reach effective concentration in the cord. Our minimal effective dosage was 0.05 mgm./kgm. Winder, Winder and Gesell (1933) obtained an increase in respiration from intravenous injection of cyanide in anaesthetized dogs after carotid sinus and vagus nerves had been put out of action with a minimal dose of 0.03 mgm./kgm. It is somewhat surprising, perhaps, that an effect on the spinal reflex can be demonstrated with a concentration of cyanide so close to that affecting the respiratory center.

Experiments with increased intraspinal pressure

Cushing (1901) showed that increased intracranial pressure caused the blood vessels in the brain to diminish in size, sometimes to the point of

invisibility, with resultant symptoms of brain asphyxia. We have modified Cushing's original method to limit sharply the asphyxia to the cord. A plug of fine-grained sponge rubber is forced into the neural canal in the neck and a hypodermic needle connected with a pressure bottle of Ringer's solution is inserted either through the rubber plug, or more commonly between the last lumbar and first sacral vertebrae. The pressure bottle is then raised, usually

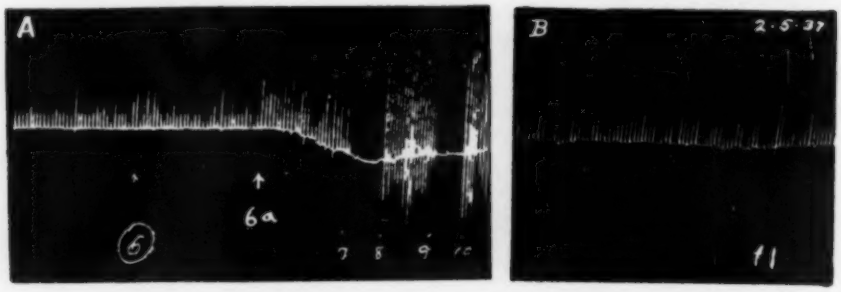


FIG. 2. Intravenous injections of cyanide in the spinal cat cause spread of reflex action within the reflex center, but not direct stimulation of motor neurones.

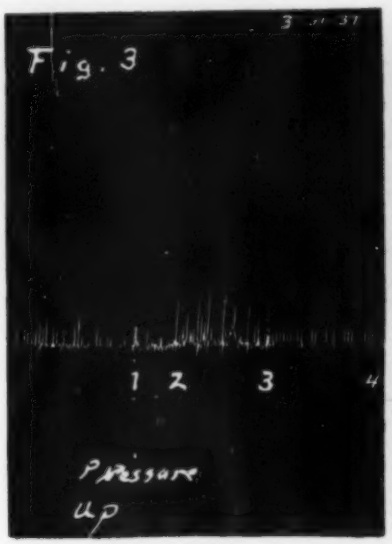
Record A. Reflex contractions of tenuissimus. Break shocks to posterior tibial nerve 45 per minute. Strength of shocks unchanged during the record. From 1 to 4 motor units (most frequently 2) in activity at first. At 6 an intravenous injection of cyanide, 0.4 mgm./kgm. At 6a a spread of reflex activity to an increased number of motor units. Between 7 and 8, and between 9 and 10, stimuli discontinued with resulting quiescence of the muscle, indicating that the cyanide has not been stimulating motoneurones directly, but facilitating reflex action. (The drop in base line following 6a is due to incipient convulsive movements in other parts of the body.)

Record B. To show the temporary effect of cyanide. Forty-five minutes later than Record A. The reflex has returned to the contraction of mostly 1 to 3 motor units, as at the beginning of the experiment.

rapidly, until an effect is produced on the height of the reflex contractions. Pressures used have varied from 70 to 150 cm. of water. Fig. 3 records the results of such a procedure with facilitated contractions appearing after a latent period of 24 seconds. The spread of reflex activity produced by increased intraspinal pressure is not a direct stimulation of motoneurones in the reflex center for contractions only follow reflex stimulation. This is shown in Fig. 4.

The question arises as to whether the improvement in the contraction height of the tenuissimus might not have been due to some direct effect of the two procedures on the nerve-muscle mechanism instead of to a reflex facilitation, as we have maintained. Winkler (1930) and Gay (1930) believed that injection of cyanide improved contraction by this means. Cyanide might conceivably do this, but it is not easy to see how an increased intraspinal pressure could improve nerve-muscle activity except by general changes in blood pressure. Actually, cyanide invariably lowered blood pressure (34 injections in 4 cats gave falls ranging from 4 mm. Hg.—initial pressure 35—to 22 mm. Hg.—initial pressure 57) and increased intraspinal pressure raised it (33

tests on 3 cats ranged from 2 mm. Hg. rise—initial pressure 74—to 76 mm. Hg.—initial pressure 74). One might imagine that the low pressure produced by cyanide was accompanied by vaso-dilatation in the muscle with improvement in contraction, or that the increased blood pressure following raised



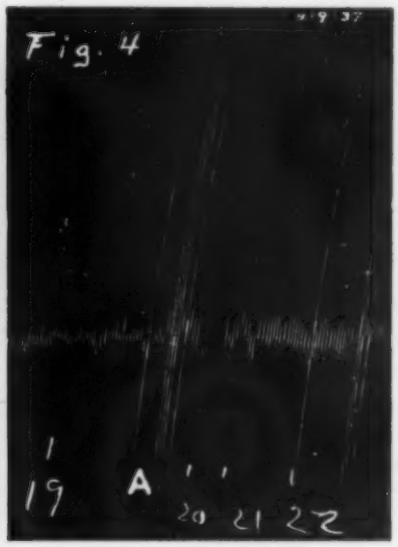


FIG. 3. Increased intraspinal pressure in the spinal cat results in increased height of reflex contraction of the tenuissimus muscle. Single shocks to posterior tibial nerve, unchanged in strength during the record. Record natural size. Magnification of muscle contraction about 15 times. Contractions at first involve 1 to 3 motor units, occasionally more. At 1 pressure bottle raised—height not noted—and bottle not lowered during the portion of record shown. At 2 the contractions involve additional motor units. Between 3 and 4 spread of reflex action indicated by greater regularity of second motor unit.

FIG. 4. The increased height of reflex contraction of tenuissimus muscle following increased intraspinal pressure is a facilitation, not a direct stimulation of motoneurones. Contractions at first involve 1 or 2 motor units. At 19 pressure bottle raised (amount not noted) and intraspinal pressure increased. At A spread of reflex action to third motor unit (unusually high in this animal) and greater regularity of second. Between 20 and 21 the stimuli were discontinued, and reflex contractions ceased. Hence, intraspinal pressure was not stimulating motoneurones, but facilitating synaptic conduction. At 22 bottle lowered. Record natural size. Magnification of muscle contraction about 25 times. (Undulations in base line due to artificial respiration.)

intraspinal pressure led to a more rapid blood flow through the muscle, again with improvement in contraction.

The question of a possible direct effect of these procedures on nerve or muscle has been tested by cutting and stimulating the sciatic at the origin of the nerve to the tenuissimus after obtaining effects on the reflex. As seen in Fig. 5, and all experiments give like results, a dose of cyanide which greatly increased reflex contractions had no effect when repeated while the cut motor nerve was stimulated with supraminimal shocks.

A similar procedure has been employed to show that increased intraspinal pressure does not result in changes in the nerve-muscle preparation (Fig. 6). There is no improvement in contraction of the muscle when it is a part of a nerve-muscle preparation—at least in the sense of new motor units entering

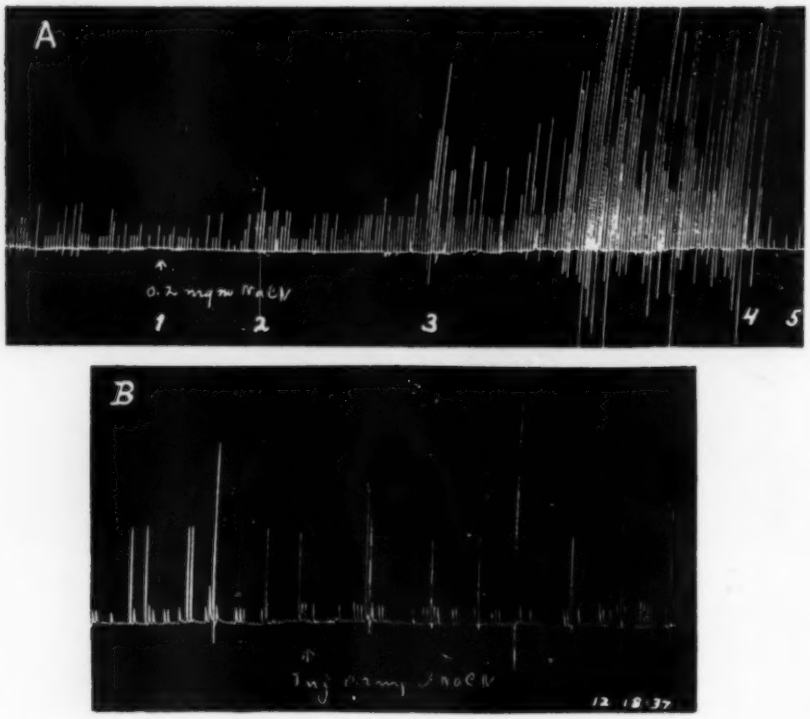


FIG. 5. Injections of cyanide affect only the reflex, not the nerve-muscle preparation.

Record A. Reflex contractions of tenuissimus from break shocks, 45 per minute, unchanged in strength during the record, applied to the posterior tibial nerve. Contractions at first mainly 1 motor unit high. At 1 an injection of sodium cyanide 0.05 mg./kgm. At 2 reflex activity spreads to include three motor units. Between 3 and 4 spread has become so extensive that it often is impossible to say how many motor units are involved. Between 4 and 5 the reflex contractions are involving again only 1 to 3 motor units, as at the beginning of the record.

Record B. The tenuissimus has been made a nerve-muscle preparation. An injection of cyanide equal in amount to that of record A produces no change in the number of motor units in activity. (Record B 2 hours 15 minutes later than record A.)

activity. In a few instances in nerve-muscle preparations the contraction of such motor units as were already in activity seemed improved following increased intraspinal pressure, never after injection of cyanide. This improvement is slight, occurs after the intraspinal pressure has been returned to normal, and is presumably referable to the increased blood pressure, but we have no data on that point.

In the present state of knowledge with regard to phenomena occurring within the spinal cord (cf. Forbes, 1936), it is, perhaps, futile to speculate on how asphyxia of the cord operates to cause spread of reflex action. It is not obvious how a neuro-humor within the center would be chemically

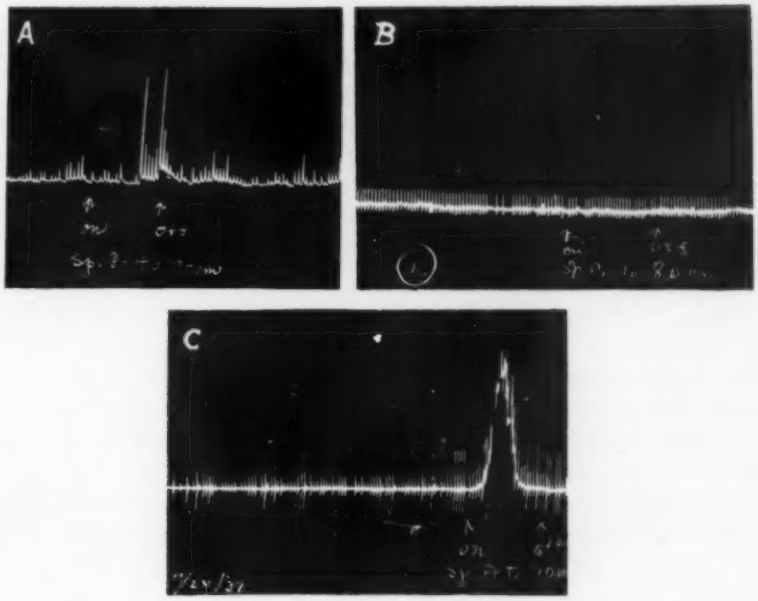


FIG. 6. Increased intraspinal pressure in the spinal cat improves reflex contractions only and has no effect on the nerve-muscle preparation.

Record A. Reflex contractions of tenuissimus with 1 to 3 motor units in activity at first. Between "on" and "off" the intraspinal pressure was increased, causing transient spread of activity to more motor units. On removal of increased intraspinal pressure reflex promptly returns to approximately the original height.

Record B. Tenuissimus now a nerve muscle preparation with only one motor unit in activity. Increased intraspinal pressure between the arrows had no effect on the height of contraction.

Record C. Same conditions as B, but the intraspinal pressure carried to a point such that convulsive movements elsewhere in the animal, indicating asphyxial effects on the cord, caused a rise in base line of the tenuissimus nerve-muscle preparation, but there is no change in height of tenuissimus contractions measured from this base line. Stimulation unchanged during each record. Magnification of contraction on drum about 15 times.

changed or cell surfaces at synaptic junctions be altered by oxygen lack. It is interesting, however, in this connection that Brinley (1928) finds that cyanide paralyzes ameba only when applied to the surface, not when injected into the protoplasm. But in any event, it seems clear that facilitation occurs in consequence of slight asphyxia of the cord, and it would appear that in formulating a theory of the nature of synaptic conduction this fact should not be lost sight of.

Summary and Conclusions

(1) A method is described by which the reflex contractions of the tenuissimus muscle in the spinal cat are used as an indicator of the state of activity of its reflex center.

(2) This indicator is so delicate that the entrance into or exit from activity of individual motor units can be seen. Depression in the center is shown by a diminution of the number of motor units in activity; facilitation by an increase.

(3) Slight asphyxia, caused by the intravenous injection of sodium cyanide, increases the number of motor units responding to the same strength of sensory stimulus as before.

(4) The increased response is not a direct stimulation of motoneurones because no contraction occurs if sensory stimulation is discontinued during the period of increased contraction.

(5) Asphyxia, produced by increased intraspinal pressure, acts similarly.

(6) Both procedures cause changes in blood pressure in the spinal cat—cyanide a lowering and increased intraspinal pressure a rise.

(7) Neither injections of cyanide nor increased intraspinal pressure cause new motor units to enter into the contraction when the tenuissimus is used as a nerve-muscle preparation.

(8) It is concluded that the first effect of asphyxia, whether produced by the injection of cyanide or by increased intraspinal pressure, is the facilitation of reflex action, as shown by the spread of activity within the reflex center to motor units which were formerly not in activity.

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THE DIRECT FUNCTIONAL INTERRELATION OF SENSORY CORTEX AND OPTIC THALAMUS*†

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INTRODUCTION

THE OPTIC thalamus is the last subcortical relay-station for all corticipetal sensory‡ systems. From its lateral, ventro-lateral and ventral nuclei originate the thalamo-cortical neurons to terminate in the sensory cortex. However, these nuclei are connected with the sensory cortex not only through these corticopetal fibers but also through innumerable corticofugal neurons, beginning in the sensory cortex and ending in these very same thalamic nuclei.[8] These two-way connections indicate a close functional interrelation between thalamus and sensory cortex. This interrelation was proposed first in 1911 by Head,[6] who, to explain the spontaneous pains and hypersensitivity of the skin freqently a component of the "thalamic syndrome," advanced the hypothesis that cortico-thalamic impulses inhibit thalamic activity. On the basis of his experiments with local strychninization of the monkey's cortex Dusser de Barenne in 1924[1] advanced two hypotheses, 1. that such strychninization "sets on fire" a much larger portion of the sensory cortex than the area strychninized, 2. that under these conditions the corresponding thalamic nucleus also is "fired" (l.c. p. 285 et seq.). The first of these hypotheses has been verified and amplified recently.[4] In this paper we bring the verification of the second hypothesis.

Inasmuch as the local strychninization§ anywhere in the sensory cortex produces "strychnine-spikes" in the electrocorticogram (ECG) of functionally related areas,[4] it was plausible to expect that the same local strychninization of this cortex might also "fire," i.e., produce strychinine-spikes in the electrothalamogram (ETG) of the related thalamic nucleus or nuclei. If this surmise proved to be correct, one would have here a physiological method for the investigation of the direct cortico-thalamic functional relations. To attack this problem it was necessary to know in which thalamic nucleus or nuclei the face, arms and legs are represented sensorially, i.e., to know the

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† The main result of this investigation was first presented as part of a symposium on "The Cerebral Cortex and Behavior" before the Section on Psychology of the Amer. Assoc. for the Advancement of Science at its Atlantic City Meeting, December 30, 1936. See *Amer. J. Physiol.*, 1937, *119:* 263 and Communications XI. Congrès international de Psychologie, Paris, July 1937.

‡ In this paper the term "sensory" is applied to all nervous structures mediating sensation (exteroceptive, proprioceptive—perhaps interoceptive), other than vision, audition, olfaction and gustation.

§ With local strychninization is meant that the strychnine solution is applied to a few square millimeters of cortex.

functional localization in the thalamus of the monkey. This localization was established in 1934–1935 by intrathalamic strychninization, in combination with "clinical" observation of the ensuing sensory disturbances.[3]

Once this functional localization was known the experiments to be reported in this paper were, in principle, very simple: concentric needle-electrodes were introduced into a particular nucleus of the thalamus and the ETG recorded before and after the local strychninization of the various subdivisions of the sensory cortex.

These experiments have established the following, direct functional relation of the sensory cortex to the thalamus: each thalamic nucleus is "fired" by the local strychninization of that, and *only* that, subdivision of the sensory cortex which subserves sensation of the *same* part of the body.

A second group of experiments in which the ECG of the various subdivisions of the sensory cortex was taken before and after intrathalamic strychninization, has shown the following direct functional relation of the sensory nuclei of the thalamus to the sensory cortex: the injection of strychnine into any particular sensory thalamic nucleus "fires" that, and *only* that, subdivision of the sensory cortex which subserves sensation in the *same* part of the body.

METHOD

All experiments were performed on Macaque monkeys (macaca mulatta), fully anaesthetized with Dial (Ciba)*; .45 cc. per kilogram body weight, part of the dosis given intraperitoneally, part of it intramuscularly. Then the animal was tied down upon the operating-table with its head fixed in a special headholder[3] so that the head was oriented in a definite, constant position in space. One sensori-motor cortex was then exposed, and with the micro-injection apparatus of Dusser de Barenne and Sager[2,3] concentric needle-electrodes mounted on the barrel of a tuberculine-syringe, were introduced into the desired thalamic nucleus. The needle-electrodes consisted of a hypodermic needle (gauge no. 25), with its tip ground off conically, through which passed the central wire-electrode insulated to its tip. The central electrode protruded about 1½ mm. beyond the circumferential one. For recording the ETG the needle-electrodes were connected to a D.C. amplifier and cathode ray oscillograph. After taking the normal ETG the three subdivisions of the sensory cortex were locally strychninized, seriatim, ending with the subdivision functionally related to the thalamic nucleus into which the needle had been introduced. An ETG was taken after each strychninization. The experiment was repeated on the opposite hemisphere. Then the animal was killed by injection of 100 cc. of 15% formalin into each of the carotids. Half an hour later the brain was removed and placed in formalin; 15–20 hours later the brain was sectioned (in the frontal plane) in slices 2 mm. thick and thus the location of the needle in the thalamus identified. In the second group of experiments the ECGs were taken simultaneously with bipolar electrodes from the various subdivisions of the sensory cortex (A.C. amplifiers, 4-element Westinghouse oscillograph), before and after intrathalamic strychninization. This was performed as described by Dusser de Barenne and Sager.[3]

The nomenclature of the thalamic nuclei used here, as in the paper by Dusser de Barenne and Sager, is that of C. Vogt[9] and Friedemann.[5] This choice is purely for the practical reason that these authors have provided the most complete series of illustrations of the cercopithecus' thalamus. There is no objection against this choice for the experiments on the macaque's brain since Le Gros Clark and Boggon[7] have found that "the cytoarchitecture of the thalamus of Macaca corresponds extremely closely with that of *Cercopithecus* as described and figured by Friedemann (1911–12)." For the designation of the various cortical areas used here we refer to a previous paper.[4]

* The Dial was kindly put at our disposal by the Ciba Co.

Results

We shall begin with two experiments on nucleus Vb, in which the face alone is represented sensorially.[3]

Protocol of an experiment with strychninization of the postcentral cortex.

November 18, 1936. Macacus. 2.82 kg.
9.00 a.m.—1.3 cc. Dial ($\frac{2}{3}$ of the dose intraperitoneally, $\frac{1}{3}$ intramuscularly).
Exposure of *right* hemisphere. Concentric needle-electrodes into thalamus by transverse route, intended to reach nucleus Vb (face-nucleus), inclination 35°, depth 16½ mm. Central electrode to grid of amplifier, circumferential electrode (needle proper) to cathode.

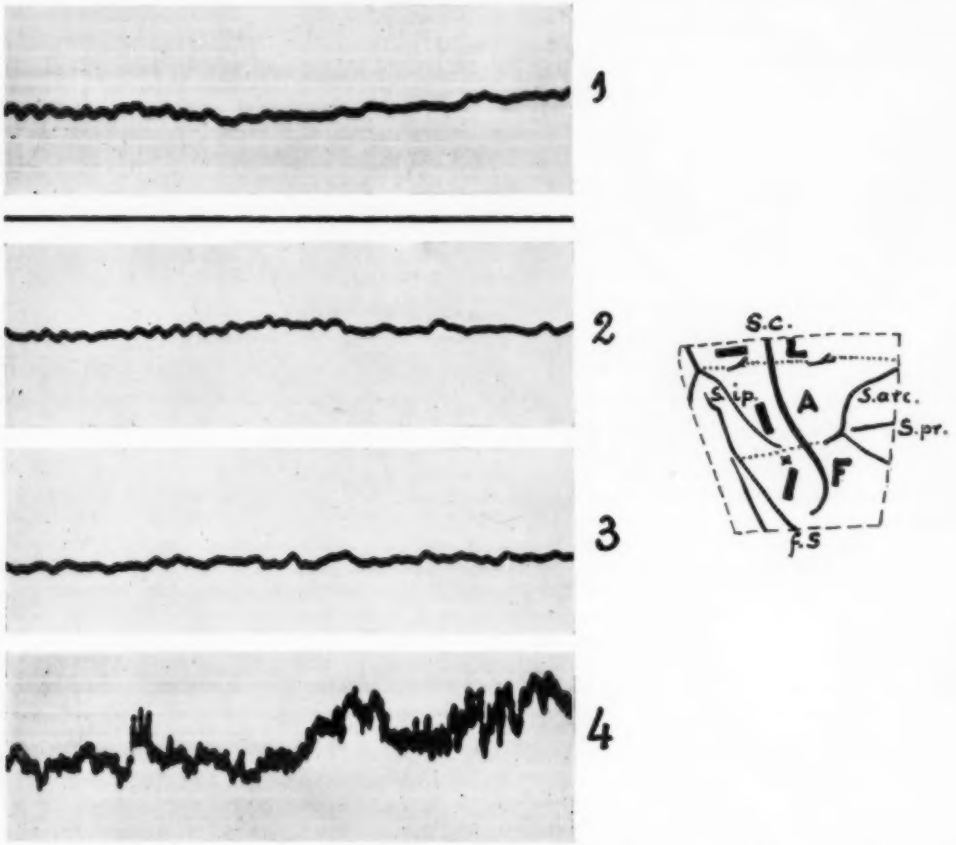

Fig. 1. Experiment of November 18, 1936. Macaque monkey. Dial narcosis. Electrothalamogram (ETG) recorded from nucleus Vb (face-nucleus). Record 1—control. Record 2—10 minutes after strychninization of postcentral leg-area. Record 3—10 minutes after strychninization of postcentral arm-area. Record 4 —13 minutes after strychninization of postcentral face-area. Only in record 4 ETG shows "firing" of face-nucleus. Amplification in all records the same. Diagram indicates location of the 3 strychnine-applications and the site of entrance of the needle (x). The stippled lines indicate the boundaries between leg- and arm- (L and A) and arm- and face-subdivisions (A and F) of the exposed portion of the sensory cortex. Broken line indicates edge of opening in dura. S.c. = sulcus centralis; s.ip. = sulcus intraparietalis; f.S. = fissura Sylvii, s.arc. = sulcus arcuatus; s. pr. = sulcus principalis.

D.C. amplifier in combination with cathode ray oscillograph. Cambridge moving paper camera.

10.55. Record 1 (Fig. 1) taken with lowest amplification.

10.57. Strychninization of *post*central *leg*-area by applying across its width an oblong piece of filter paper, moist with 3 per cent strychine-solution (dimensions of filter paper 1 × 3 mm.).

11.07. Record 2 (Fig. 1) taken.

11.11. Strychninization of *post*central *arm*-area by application of a similar strip of filter paper to lower half of postcentral gyrus, parallel to central sulcus.

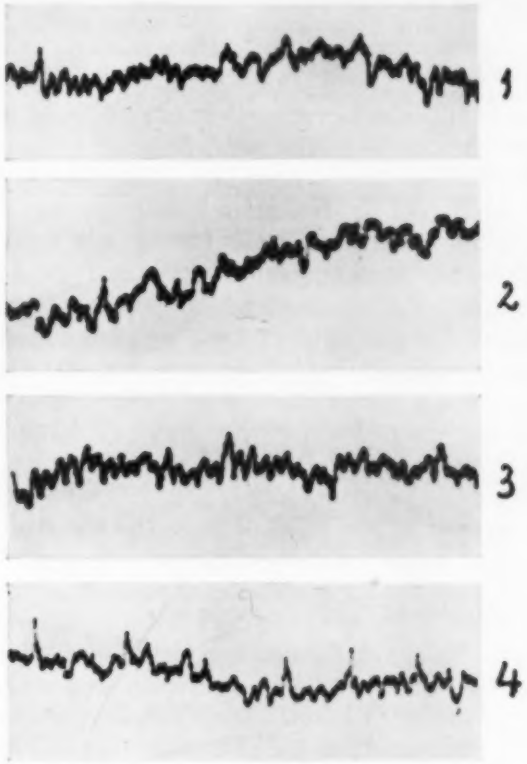

FIG. 2. Experiment of November 23, 1936. ETG of nucleus Vb_2 (face-nucleus) of thalamus of macaca mulatta (Dial-narcosis) before (record 1) and after (records 2, 3 and 4) local strychninization of precentral sensory cortex, leg-, arm- and face-areas respectively. No apparent change in ETG of records 2 and 3 compared with that of record 1; definite "firing" in ETG in record 4, i.e., 11 minutes after local strychninization of precentral face cortex.

11.21. Record 2 (Fig. 1) taken.

11.23. Strychnine applied to *post*central *face* cortex.

11.36. Record 4 (Fig. 1) taken.

Autopsy: end of needle-track in nucleus Vb at level of Vogt's plate no. $5^{9,3}$.

In the following experiment the strychninizations were performed on the precentral sensory cortex.

November 23, 1936. Macaca mulatta. 2.80 kg.

9.15 a.m. 1.3 cc. Dial($\frac{2}{3}$ of dose intraperitoneally, $\frac{1}{3}$ intramuscularly).

11.30. Animal not fully under. .1 cc Dial intramuscularly.
2.00 p.m. Animal completely anaesthetized.
2.16. Exposure of *right* hemisphere. Concentric needle-electrodes into thalamus via transversal route, intended for nucleus Vb; inclination 35°, depth 20½ mm.
2.19. Record 1 (Fig. 2) taken (amplification 3).
2.21. Strychninization of *pre*central *leg*-area with filter paper 1×3 mm.
2.32. Record 2 (Fig. 2) taken (same amplification as before).
2.33½. Strychninization of *pre*central *arm*-area 4 with filter paper 1×3 mm.
2.40. Record 3 (Fig. 2)taken (same amplification).
3.09. Strychninization of *pre*central *face* cortex with filter paper (1×3 mm.) moistened with 3 per cent strychnine solution.
3.20. Record 4 (Fig. 2) taken (same amplification as before.)
November 24. *Autopsy:* needle-track ends in plane between C. Vogt's plates 5 and 6 in nucleus Vb_2.

From these two and similar experiments it follows (1) that the local strychninization of the face-subdivision of the sensory cortex results in typical changes in the ETG of the face-nucleus (Vb); (2) that the local strychninization of any portion of the two other subdivisions of the sensory cortex does not produce any changes in the ETG of this nucleus; (3) that this nucleus is "fired" by the local strychninization of the precentral as well as of the postcentral portion of the face-subdivision of the sensory cortex.

The same obtains for the arm- and leg-nuclei, i.e., that each is "fired" only by the local strychninization of the pre- or postcentral portion of the subdivision of the sensory cortex corresponding to it.

There is one point which needs further elucidation, namely the apparent contradiction which was mentioned in our paper on "functional organization in the sensory cortex of the monkey" (4, p. 83). There it was reported that strychnine-spikes appear in the ECG of both the leg- *and* arm-subdivisions of the sensory cortex upon local strychninization of either L.6a or A.6a. Those observations have shown that so far as this distribution of the strychninespikes in the cortex is concerned no functional boundary exhibits itself between L.6a and A.6a. However, the contrast between this absence of the functional boundary, so far as the ECG in concerned, and its presence in regard to the symptoms of sensory excitation upon local strychninization of these same areas is not a contradiction, for the ECG expresses the activity of the cortex at that level of the CNS, whereas the symptoms of sensory excitation depend upon lower levels, notably the sensory nuclei of the optic thalamus, upon which converge all sensory impulses from the periphery of the body. At present we know that local strychninization of the sensory cortex "fires" the sensory nuclei of the thalamus, and in this respect one finds a definite functional boundary between L.6a and A.6a, for the leg-nuclei are "fired" by local strychninization of L.6a, but not by that of A.6a, whereas the arm-nuclei are "fired" by local strychninization of A.6a, but not by that of L.6a.

The following protocol serves as an illustration.

November 30, 1936. Macaca mulatta. 3.38 kg.
9.10. 1.52 cc. Dial (⅔ of dose intraperitoneally, ⅓ intramuscularly).
10.00. Animal completely under.
10.02. Exposure of *right* hemisphere.
10.05. Concentric needle-electrodes into thalamus via transversal route. Intention to

reach the dorsal portion of one of the arm-nuclei, lbIV or lbI (C. Vogt), inclination 33°, depth 19 mm.

10.25. Record 1 (Fig. 3) taken (control) and then a series of records from various areas of the leg- and arm-subdivisions of sensory cortex.

10.37. Local strychninization (1 ×3 mm.) of *leg*-area 6a (L.6a).

10.44. Record 2 (Fig. 3) taken with same amplification as in record 1. Subsequently a series of records from various areas of sensory cortex was taken (L.6a, L.4, L.2, A.6a, A.4, A.2, L.6a).* Needle left in thalamus until afternoon.

2.31. Record 3 (Fig. 3) taken as a control.

2.40½. Local strychninization of *arm*-area 6a (A.6a).

2.45. Record 4 (Fig. 3) taken, followed by recording of ECG of various areas of the leg- and arm-subdivisions.*

December 1.

Autopsy: End of needle track in dorsal portion of nucleus lbI (Vogt's plate 6(arm nucleus)). *Conclusion:* local strychninization of L.6a did not "fire" this nucleus, whereas local strychninization of A.6a promptly "fired" this nucleus. Following the strychninization of L.6a (morning) and that of A.6a (afternoon) both entire leg- and arm-subdivisions were "fired."

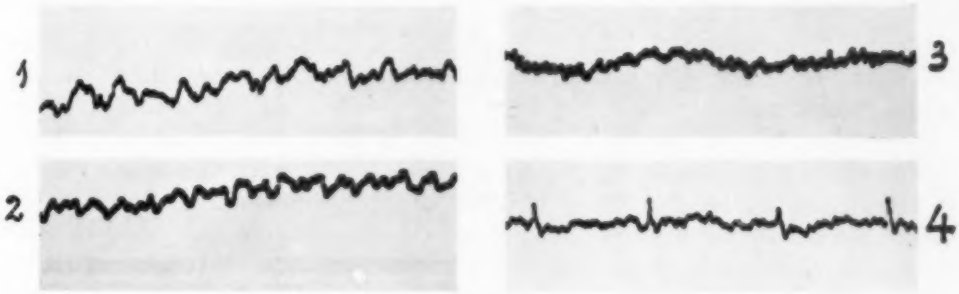

FIG. 3. Experiment of November 30, 1936. ETGs of nucleus lbI (one of the arm-nuclei) of macaque's thalamus. Dial-narcosis. Record 1 taken before, record 2 after local strychninization of L.6a. No change in ETG. Record 3 taken before, record 4 after local strychninization of A.6a. Prompt "firing" of nucleus lbI. The entire leg- *and* arm-subdivisions were fired by *each* of the two strychninizations.

The second group of experiments mentioned above rounds out the picture of the direct functional interrelation of sensory cortex and thalamus. In these experiments intrathalamic strychnine-injections were performed, using the micro-injection technique described previously,[2,3] and recording the ECG of various areas of the three subdivisions of the sensory cortex. The essential result in this group was that the injection of strychnine into any particular sensory nucleus of the thalamus "fired" that, and *only* that, subdivision of the sensory cortex, both precentral and postcentral, which subserves sensation in the *same* part of the body. This result must be interpreted as showing that in each particular nucleus of the thalamus, let us say, in each arm-nucleus originate thalamo-cortical neurons to terminate in the various areas of the arm-subdivision, and only of the arm-subdivision, of the sensory cortex; thus the strychninization of the perikarya of these neurons "sets on fire" the various areas of the arm-subdivision of the sensory cortex. The same re-

* This part of the protocol considerably reduced.

lation obtains between the leg- and face-nuclei of the thalamus and the leg- and face-subdivisions of the sensory cortex respectively.

Finally it must be stated that (1) local strychninization of white matter (e.g., corona radiata, internal capsule, corpus callosum) in our experience never "fires" grey matter; (2) local strychninization of masses of grey matter having no direct corticipetal connections with the sensory cortex (e.g., nucleus caudatus, medial nuclei of the thalamus) never "fires" this region of the cortex.

Discussion

Apart from the results, reported above, to which we shall return below, these experiments provide a check upon the extent, location and subdivision of the sensory cortex on the outer surface of the macaque's brain,[1] and upon the functional identification of the macaque's sensory nuclei in the thalamus.[3] In this connection two crucial findings should be reported here: 1. local strychninization *without* the sensory cortex never "fired" the face-, arm- or leg-nuclei of the thalamus; 2. local strychninization anywhere *within* the sensory cortex never "fired" the *medial* nuclei of the thalamus (mag, mapt, mapl, maga, magp, mα).

Together, all the results of the present investigation are in entire harmony with the results of the previous work and complete the confirmation of the two hypotheses advanced in 1924[1] to explain how strychninization of only a few square millimeters of the sensory cortex induces symptoms of sensory excitation in a large portion of the body. That local strychninization of grey matter in the CNS with recording of the electrical activity of grey matter in the CNS reveals directed functional relations has been shown in a previous paper.[4] Therefore, the only construction which can be put on the facts here established by *physiological* methods is that there exist between the sensory cortex and the sensory nuclei of the thalamus directed functional relations: 1. from each subdivision of the sensory cortex to, and only to, the corresponding sensory thalamic nucleus or nuclei, 2. from each sensory thalamic nucleus to, and only to, the corresponding subdivision of the sensory cortex. This is schematized in Fig. 4.

The three principal features in this diagram are:

1. the essential similarity of the three sensory systems for face, arms and legs;
2. that each system after reaching the cortex feeds back into the thalamus;
3. that throughout the entire course of these three systems functional boundaries are maintained.

The diagram shows these boundaries only for one frontal plane, but it must be pointed out that they are present throughout the entire fronto-occipital extent, both in the thalamus and in the cortex. Thus the boundary indicated in the diagram between the leg- and arm-subdivisions of the sensory cortex extends all the way from the interparietal sulcus to the anterior

margin of area 6a, as represented in the diagrams of the extent, location and subdivision of the sensory cortex previously given.[1,4]

The apparent contradiction mentioned on p. 180 leads to an important point. Two observations are relevant here:

1. So far as the cortical distribution of the strychnine-spikes in the leg- and arm-subdivisions upon local strychninization of L.6a or A.6a is concerned, no functional boundary between the two subdivisions exhibits itself.

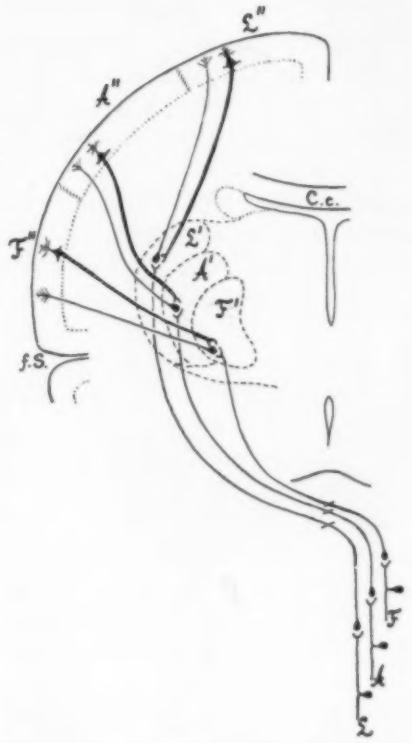

FIG. 4. Diagrammatic representation of the organization of the three main sensory systems (for the legs, arms and face). All internuncial neurons between the subthalamic sensory neurons and the thalamo-cortical neurons have been omitted, to simplify as much as possible the diagram.

2. Notwithstanding the fact that both entire leg- and arm-subdivisions of the sensory cortex are "fired" by local strychninization of either L.6a or A.6a, an animal, when "clinically" observed (without narcosis), discretely refers his symptoms of sensory excitation (paraesthesiae, hyperaesthesia and hyperalgesia) to the legs, and *only* to the legs, after local strychninization of L.6a, and conversely to the arms, and *only* to the arms, after local strychninization of A.6a.

These observations throw new light on the observation of Dusser de Barenne and Sager that the symptomatology after local intrathalamic strych-

ninization in the acutely and totally decorticated cat was indistinguishable from the symptomatology in the animal with cortex intact. From that observation the authors concluded that in the case of strychninization of the thalamus "the sensory cortex plays no role in the elaboration of the ensuing sensory disturbances" (2, p. 246).

In this respect the cortex is (in the cat) not only unnecessary but is even unable (in the monkey!) to distort the distribution of the sensory disturbances determined by the hyperactive thalamic nucleus or nuclei. The functional boundaries remain. For the "firing" of the two entire leg- and arm-subdivisions of the sensory cortex by local strychninization within either L.6a or A.6a does not deter the animal from projecting his sensory disturbances discretely upon that part of the body subserved sensorially by the particular thalamic structure "fired" by the feed-back from the strychninized cortical area.

It follows that the part of the body to which the animal refers his symptoms of sensory excitation is determined *not* by the subdivision or subdivisions of the sensory cortex "fired," but by the thalamic nucleus or nuclei "fired" by the direct feed-back from the strychninized area of the sensory cortex.

Thus, though both hypotheses advanced by Dusser de Barenne in explanation of his observations in 1924 have been substantiated, the second hypothesis, namely that local strychninization of any subdivision of the sensory cortex "sets on fire" the corresponding thalamic nucleus or nuclei, is evidently the crucial one. For all these observations and considerations imply not only the predominance of the thalamus in sensation, but that this last subcortical sensory station determines the reference of sensation by the individual, even contrary to coexisting cortical activity.

We must now discuss briefly the hypotheses of Head and Holmes[6] concerning the functional interrelation of the thalamus and cortex in the production of sensation.

In their well-known diagram (6, p. 172) they represent an internuncial neuron from the ventro-lateral region of the thalamus to the medial nuclei, which they regard as the "essential center" of the thalamus. The cortico-thalamic neurons ending in the ventro-lateral region of the thalamus exert, according to Head and Holmes, an inhibitory influence upon this region of the thalamus. They assume that with interruption of these cortico-thalamic fibers the activity of the thalamus is released from its normal cortical restraint, and that the afferent impulses, reaching the ventro-lateral region of the thalamus, flow over uncontrolled to the medial thalamic region, which "is the centre of consciousness for certain elements of sensation" (l.c. p. 181), "mainly occupied with the affective side of sensation" (l.c. p. 180).

This attractive conception, however, is open to criticism. Although in the cat the medial nuclei are endowed in some way with sensory functions[2], this is not so in the monkey[3]. Apparently in this respect evolution of thalamic structures and functions has resulted in a definite shift. It is highly

improbable that in the evolution of the human brain phylogeny should have reversed itself, backward toward the stage of the cat instead of onward from the stage of the monkey. In the second place the inhibitory function of the cortico-thalamic pathways is by no means established; in fact it was and is purely hypothetical. In all experiments presented here the strychninization of a number of the cells of origin of these cortico-thalamic neurons in the sensory cortex resulted in a "firing" of the corresponding thalamic nuclei, just as, in the earlier experiments of Dusser de Barenne[1], it resulted in symptoms of sensory excitation. These are results which are the reverse of what could be expected on the basis of the hypotheses of Head and Holmes. Yet there may be some truth in them, for we have found that the local strychninization of two particular regions, areas 4-s and 1, of the monkey's sensory cortex results in a temporary suppression of the electrical activity of area 4[4]. However, this suppression in the case of area 4-s does not depend upon the direct cortico-thalamic connections which Head and Holmes had in mind and with which the present paper dealt. This suppression involves indirect cortico-thalamic relations and must be taken up in a subsequent paper.

Summary

The present paper deals with two groups of experiments:

1. the effect of local strychninization of the sensory cortex upon the electrical activity of the optic thalamus, i.e., upon the electrothalamogram (ETG),

2. the effect of local strychninization of the sensory thalamic nuclei upon the electrical activity of the sensory cortex, i.e. upon its electrocorticogram (ECG).

In the first group with local strychninization of the cortex it was found that each thalamic nucleus is "fired" from that, and only that, subdivision of the sensory cortex, subserving sensation in the same part of the body. In the second group of experiments it was found that local strychninization of any particular sensory thalamic nucleus "fires" that, and only that, subdivision of the sensory cortex which subserves sensation in the same part of the body.

Sharp functional boundaries exhibit themselves between the adjoining sensory systems.

The discussion indicates the significance of these observations in regard to the dominance of the thalamus over the sensory cortex in sensory disturbances, even when initiated by excitation from the sensory cortex.

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